

It takes more severity than many mothers can command to force spinach upon a tearful child Yet careful menu planning is needed to make up the 12 mg of iron required daily Leich enring and Flor, as an example found that children's diets planned to contain 5 and 8.5 mp from actually supplied only 3.25 and 6.5 mg, respectively although the diet was designed to provide a high from intake and included such foods as misins carrots, graham bread prunes, lettuce, beef, and

LIKE SPINAC

## PABLUM tastes good

## AND IS 566% RICHER IN IRON

PABLUM is a food that children really like and take willingly Added to this virtue, it supplies known amounts of iron—more than any other food of equal calone value! This unique pre-cooked cercal contains 566% more iron than fresh spinach with an iron content of 36 mg<sup>2</sup> (The U S Dept of Agriculture reports an even lower average for spinach—25 mg<sup>3</sup>) When included in the child's daily diet from the third month on, Pablum is a valuable prophylactic against nutrition il anemia. Besides the hemoglobinbuilding element, iron, Publim contains copper and substantial amounts of calcium, phosphorus, and vitamins A, B, L, and G Abundant, too, in calories, proteins, fat, and earbohy drates

1-3 Billiography on request

For a Delicious Cercal Just Add Hot Water or Mill. (hot or cold)—Pablum Requires No Cooking

Pablum consists of wheat-meal outmeal, cornmeal wheat embryo seast alfalfa leaf and beef bane Supplies vitamins 1 B E, and G and calcium phosphorus roan capage and other second.

copper and other essential

Supplied in 1 lb eart radidue's

MEAD JOHNSON & CO, Evensville, Ind, USA Process in Vilamin

## MEAD'S VIOSTEROL IN <u>economical</u>, efficient HALIBUT LIVER OIL 250 D for vitamins A and D

TO HALIBUT liver oil which con forms to standards in New and Non official Remedies and which has been adjusted\* to contain not less than 32,000 vitamin A Units (U.S.P.X.) per gram is added sufficient viosterol (activated er gosterol) of previously determined vita min D value to assure a vitamin D potency of not less than 250 D (or 3 333 Steenbock units per gram)

#### HIGHLY POTENT IN VITAMIN A

Ten drops of Mead's Viosterol in Halibut Liver Oil 250 D offer approximately 8 000 USP vitamin A units as compared with 7,700 U.S.P vitamin A units supplied by three teaspoonfuls of cod liver oil (stand ardized at 700 USP vitamin A units per gram)

### EQUAL IN VITAMIN D TO MEAD'S VIOSTEROL

Mead's Viosterol in Halibut Laver Oil 250 D supplies the same amount of vitamin D present in Mead s Viosterol in Oil 250 D the most potent type of antiricketic commercially available It may therefore be used for the same condutions and in the same dosage as Mead's Viosterol in Oil 250 D from which it differs in that it also supplies generous amounts of vitamin A.

Three temponduls (the average daily dosne) of standardized cod liver oil containing 40 Steenbock vitamin D units per gram offer 480 units. Ten drops of Mead a Viosterol in Halibut Liver Oil 230 D supply 830 Steenbook vitamin D units (30 of these units are supplied by the halibut liver oil)

From the above comparison it may be seen that for both vitamins A and D ten drops of this product compare more than favorably with cod liver oil in dosage of three teaspoonfuls, a quantity about fifty times as much.

This results in two practical advantages (1) In cases of fat intolerance, obesity pregnancy and premature infants the small amount of fat in the average dose of Mead's Viosterol in Halibut Liver Oil 250 D may be given without gastric disturbance (2) in cases where a more-than-average

"Ty the publishes of other list five one from one or more of the following

design of vitamin D or/and vitamin A is indicated, it is possible to push the design of this product without fat intolerance whereas more than four to five teaspoonfuls of cod liver oil daily are usually impracticable.

#### BIOLOGICALLY ASSAYED

The standard of potency for vitamins A and D in Mead's Vicoterol in Halibut Liver Oil is rigidly maintained by constant bioassay. Mead Johnson and Company are fortunate in having a research laboratory with long experience in bioassays. Their background in this field extends to pioneer work with cod liver oil and vicaterol.

#### INDICATIONS

Vitamin A Deficiencies For such acute deficencies of vitamin A as aerophthalmia xerons, and hemeralopia, Mead's Viosterol in Halibut Laver Oil, when given in proper dosage, is a specific.

Since vitamin A has been held to be of value in maintaining the integrity of the mucous membranes and hence to be a sinegurard against the invasion of pathogenic bacteria, Mead's Vlosterol in Halibut Laver Ol would seem to be indicated in cases in which it is desired to provide an aid in building up general resistance to body infection At the present time, vitamin A cannot be regarded as "the anti infective vitamin."

Vitamin D Deficiencies Since vitamin D is capable of raising either the serum calcium or the serum phosphorus, depending upon which is in low concentration, Mead a Viosterol in Halibut Liver Oil is indicated where such disturbances of minoral metabolism arise. Where a rapid-acting calcifying agent is required and gastric disturbances must be reduced to a minimum, it is unsurpassed.

Mead's Viosterol in Halibut Laver Oil may be administered for all purposes in which Mead's Viosterol has proved itself valuable and has the additional advantage of offering generous amounts of vitamin A

economical for vitamin A:

Mead's Halibut Liver Oil

economical for vitamin D:

Mead's Viosterol in Oil 950 D

MEAD JOHNSON & COMPANY, Evansville, Indiana France excluse products be coperate its preventing to be translating translating process.

# The "constitutional tendency in rickets" . . . . Important

because it explains why some infants develop normally and others cannot build the right kind of bones and teeth unless they are kept on a potent source of Vitamin D such as Viosterol!

• "There is a definite constitutional tendency to rickets, quite apart from diet, hygiene and growth, say Drs Alfred F Hess and S N Blackberg (Am J Physiol 102 8, Oct 1932)

'Among infants receiving the same diet and the same care, some develop normally whereas others develop moderate or even a marked degree of rickets

For infants whose special susceptibility to rickets is high, an extremely potent antirachitic may be used routinely. These infants often fail to receive enough protection from milder measures. Imperceptibly at first, noticeably after a few months, they develop disorders of bones and teeth which may become a lasting liability.

The physician who has had wide experience with rickets is often able to recognize this tendency before the disease is fully developed. Frequently he spares infants more

serious forms of rickets by prescribing promptly as potent a source of Vitamin D as is available for use routinely—Viosterol in Oil 250 D

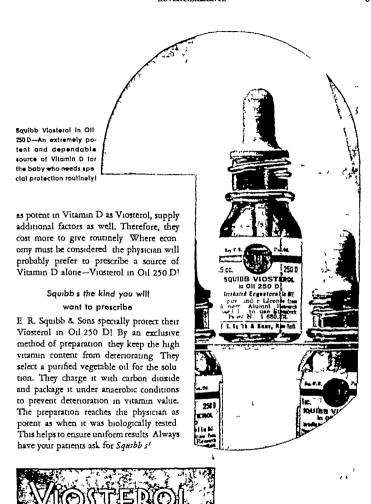
This effective agent has many features to recommend it as a prophylactic for the baby constitutionally subject to rickets

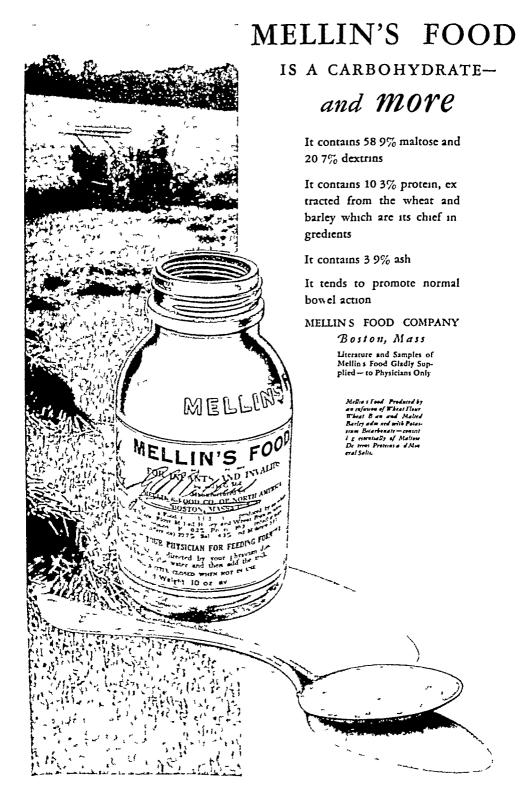
Rapid colorlying action—The large amount of Vitamin D supplied by Viosterol brings about a prompt response in mineral metabolism. This is because of the high potency. Viosterol supplies 250 times as much Vitamin D as the standard cod liver oil defined by the Wisconsin Alumni Research Foundation.

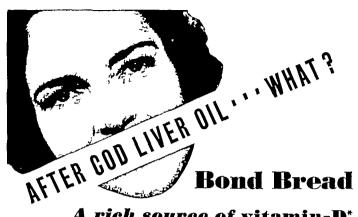
Drop dosage—Viosterol in Oil 250 D is convenient and easy to give Babics readily tolerate the few drops needed to be effective

Less expensive—Some other anti-rachitics









## A rich source of vitamin-

WHEN the prescription for infants of vita min D in the form of cod liver oil, viosterol. or vitamin D milk is discontinued isn t it important that some other source of vita min D be made available? Foremost nutri tionists agree that extra vitamin D is of val ue to adults also

If our studies and those of Mrs Mellanby are as sound as we believe they are they will afford evidence that in temperate regions people of all ages should take some source of viramin D

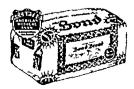
It has been our experience over a period of many years that infants and children suffering from a lack of vitamin Dhave lowered resistance against infection. This decreased resistance has been observed by the majority of the outstanding pediatricians in both the United States and Canada -Dr E. V Mc Collum

Such results (referring to other research) tend to support the impression of the value of vitamin D as a food constituent for the adult. When the vitamin is supplied in mod erate amounts in connection with either a high calcium low phosphorus rachitogenic ration or a low calcium low phosphorus ra tion calcium and phosphorus are conserved to a remarkable degree. — Journal of Ameri can Medical Association May 27 1933

As one of the necessary elements in build ing and maintaining strong bones and sound teeth an extra, easily available source of vita min D should be valuable. What daily food source fulfills these requirements better than Bond Bread?

Bibliography on request. For further information address Dr. J G Coffin Technical Director GENERAL BAKING COMPANY 420 Lexington Avenue New York City

\*Bond Bread contains vitamin D in the proportion of 95 Steenbock units to each pound of bread.



Also Bond Bakers Wheat Bread Archoth rich sources of altomin-D

# Effective LAXATIVE MEDICATION

Sodium Glycocholate \_\_\_\_ 1/4 gr Sodium Taurocholate \_\_\_\_ 1/4 gr Phenolphthalein \_\_\_\_\_ 1/2 gr Extract Cascara \_\_\_\_\_ 1/2 gr Aloin \_\_\_\_\_ 1/8 gr

TABLETS

## **OXIPHEN**

Oxiphen Tablets are particularly useful in habitual constipation because they produce gentle, yet effective laxative action throughout the intestinal tract, stimulating activity of both the secretory organs and the intestinal musculature. They may be used over extended periods without losing their



effect, and without an increase in dosage and, as normal function is re-established, the dosage may be gradually withdrawn without a return of the condition. The formula contains no toxic drugs, and does not produce the "cathartic habit"

The Oxiphen formula combines the hepatic stimulant and chologogue action of the bile salts ("the only reliable chologogue known"—Cushny) with the tonic laxative effect of cascara, the simple laxative action of phenolphthalein and the stimulant action of aloin on the colon Kindly use the coupon for literature and clinical sample

## PITMAN-MOORE COMPANY Indianapolis

PITMAN MOORE COMPANY, Indianapolis	(JP—12-33)
You may send me a sample of Oxiphen Tablets for clinical use	
	M.D
Address	
City State	

## SMA The Only Antirachitic Breast Milk Adaptation

### SO SIMPLE that even Mrs

\*can prepare it properly

### SO SIMPLE

that Mrs much worry and trouble will thank you for sparing her

( 1 N doubt you can supply names from you practice,)

## ANYONE CAN FOLLOW THESE SIMPLE INSTRUCTIONS



This proportion remains unchanged. As the infant grows older you merely increase the quantity as with breast milk. (See table below)

### SUGGESTED FEEDING TABLE

Infant	Total Quantity In 24 Hours In Ounces	No of Feedings	Pecting In Ounces
2 days 3 days 4 days 5 days 6 days 7 days	*1 to 214 ,214 to 5 15 to 714 714 to 10 10 to 1214 1214 to 15	2 to 3 3 to 4 4 to 5 5 to 7 5 to 7 5 to 7	14 to 1 12 to 114 1 to 114 1 to 2 114 to 24 2 to 3
2 weeks 4 weeks 6 weeks	15 to 1714 1714 to 20 10 to 2214	5 to 7 5 to 7 5 to 7	2 to 3 1/4 2 1/4 to 4 3 to 4 1/4
2 months 2½ months 3 months 3½ months 4 months 5 months 6 months	25 to 27 1/2 27 1/2 to 30 30 to 32 1/2 32 1/2 to 35 32 1/2 to 37 1/4	5 to 6 5 to 6 5 5 5 5	3½ to 5 4 to 5½ 5½ to 6 6 to 6½ 6½ to 7 6½ to 7½
to 1 year		5 to 4	61/2 to 10

especially spinach. \* These quantities refer to fluid ounces of 8 M A

diluted according to directions

#### TIME SCHUDULE

7 feedings: 6 9 12 3 6 9 and once during night, 6 feedings 6 9 12 3 6 and 9 or later 6 feedings 6 10 2 6 10 and 2 5 feedings: 6 10 2 6 and 10 or later 5 feedings: 6 9 12 3 and 6 or later

NUMBER OF FERDINGS IN 24 HOURS The number of feedings in 14 hours should libraries be the same as those allowed breast fed infants; generally stated not more than seven and not less than five. However when the infant reaches the age of 6 to 7 months it i customery to replace one of the feedings with an 8 ounce meal of faring broth soun

## SAVES PHYSICIAN'S TIME TOO

S. M. A. is simple to prescribe. The physician is relieved of exacting detail because he has only to increase the amount of S M A (as with breast milk) when in his judgment it becomes necessary. The accompanying chart suggests average amounts

The physician's time is also saved because the chances are good for excellent results un der his skilled supervision.

## S M A RESEMBLES BREAST MILK

S. M. A. is a food for infants-derived from tuberculin tested cows milk, the fat of which is replaced by animal and vegetable fats in cluding biologically tested cod liver oil with the addition of milk sugar potassium chloride and salts altogether forming an autirachitic food When diluted according to directions, it is essentially similiar to human milk in per centages of protein, fat carbohydrates and ash, in chemical constants of the fat and in physicial properties.

## ETHICAL OF COURSE

If babies were all alike it might not be quite so necessary to have a physician plan and supervise feedings. However from the very beginning every package of S. M. A. has carried these instructions prominently on the label. Use only on order and under supervision of a licensed physician. He will give you instructions."



S M A. CORPORATION CLEVELAND OHIO

## Anybody

can put vegetables through a sieve . BUT THERE'S MORE THAN THAT TO GERBER'S!



Ordinary commercially canned vegetables, converted for infant feeding by straining, may be "strained vegetables -but they aren t Gerber s

Gerber's vegetables are special in every sense Grown from selected seed in selected soil,

watched while growing by Gerber field supervisors, picked at the exact stage of ideal maturity, rushed crisp and fresh to the Gerber plant-Gerber's vegetables are different to start with!

And they are processed differently Scientific control is established by the Gerber research laboratory, scientific methods prevent oxidation and reduce loss of vitamin values That the resulting products are definitely superior has been confirmed by feeding experiments at Michigan State College and Columbia University, which indicate that Gerber's in minimum

quantities are adequate for normal growth, whereas ordinary products have proved inadequate

It is distinctly worth the physician s while to specify Gerber's They remove one factor of uncertainty in infant feeding

Toma ocs

Beers

Carrots

Peas Spinach cans Straintd Cereal

oz. cans

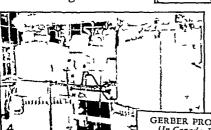
Straintd

Beans





- Hand nail and general appearance inspection twice daily Research laboratories — con trolling rigid Gerber standards 3 Sorting and inspection of gar den fresh vegetables before washing.
- 4 Vacuum cooking conserving vitamins and minerals



ercuble

Gerbei



GERBER PRODUCTS COMPANY Fremont Michigan (In Canada Fine Foods of Canada Ltd. Windsor Ont.)

Please send me | Reprint of the article | The Nutritive Value of Strained Vegetables in Infant Feeding

☐ Sample can of Gerber's Strained Cereal

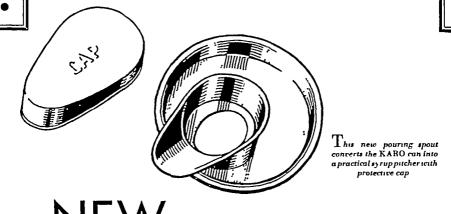
Address

State.

## Why CARITOL?

- 1 For ages, man has eaten certain palatable fruits, vegetables and dairy products to satisfy his hunger
- 2 His body requirements for vitamin A were thus un consciously satisfied in greater or less degree.
- 3 The substance responsible for this vitamin A activity has recently been shown to be carotene, a yellow organic pigment [C40H56] called Primary Vitamin A by Sherman & Smith in 1930
- 4 The prevalence of latent vitamin A deficiency diseases suggests to numerous investigators that modern diets do not contain enough carotene to fully satisfy the requirements of many individuals.
- 5 The fact that carotene is normally present in various parts of the body such as the spleen blood, lymph, breast milk corpus luteum, placenta ovaries, suprarenal glands and bone marrow would seem to indicate that in addition to its activity as a vitamin, carotene itself meets other body requirements besides its conversion into the colorless product by the liver
- 6 If this deficiency is to be made up what is more natural than to supply the same palatable substance, carotene, derived from vegetables, in concentrated form?
- 7 This is now possible. A highly potent solution contain ing 0.3% carotene [Primary Vitamin A] in oil is offered to physicians as Smaco Caritol, available at most pharmacies.
- 8 Caritol literature may be obtained from S. M. A. Corporation, Cleveland, Ohio.





# NEW...for convenience...for accurate measurement...for greater hygienic protection of KARO babies

IN KEEPING with the progressive policy of the makers of Karo Syrup, this new Karo pouring spout has been devised (1) to further safeguard the purity of Karo Syrup, (2) to make the measuring of Karo more accurate and convenient, (3) to provide insurance against contamination.

Your patients will be glad to know about this new feature Despite the costliness of the new spout, the price of KARO remains the same.

The KARO pouring spout may be obtained without cost by addressing the manufacturer

Year after year KARO enjoys greater acceptance by the medical profession. Its value as a practical carbohydrate in the modification of milk for infant feeding is now universally recognized

#### FREE TO PHYSICIANS



# NO FISHY TRITE because they contain the PALATABLE

## FRUIT AND VEGETABLE FORM OF VITAMIN A

## CARITOL, for A, alone-

Caritol is a 0.3% solution of Carotene (C<sub>oc</sub>H<sub>sc</sub>) the palatable fruit and vege table form of vitamin A, and therefore represents the

form in which most vitamin A is naturally consumed by the human body

## Helps Build Resistance and Promotes Growth

Caritol, by virtue of its vitamin A acti vity promotes growth and, as indicated by experimental studies may be an aid toward the establishment of resistance of the body to infections in general. It may be prescribed alone or with CAPSULES OR DROPS other vitamin products. There is INSTEAD OF no fishy taste or bad after taste. The cost is reasonable too Cantol is available in 15 cc and 50 cc FASY DOSES dropper top bottles and in capsules IO FISHY TASTE TZAT STITA CA packed 25 and 50 to the box

## CARITOL-with-Vitamin D

Caritol with Vitamin D is the most palatable combin ation of vitamins A and D on the market because it contains the fruit and vege

table form of vitamin A, carotene, and a tasteless vitamin D prepared for them peutic use by methods (Zucker process) developed at Columbia University It is naturally palatable, not artificially flavored.

## For A and D, together in Palatable Form

Cantol with Vitamin D is therefore especially recommended for patients who need both vitamins A and D but object to the fishy taste of fish liver oils and their concentrates

There is no fishy taste or bad after taste, and the cost is reasonable. Available at prescription pharmacies in 5 c.c. and 50 c.c. dropper top bottles and in 25 capsule boxes

Prescribe these naturally palatable vitamin products - they cost no more.

Taste the carotene products yourself. Write for samples. We also offer Smare Cad Liver Oil fertified with carotens and vitamiu D for those physicians who prefer to prescribe cod liver oil. It is three times as potent in both vitamins A and D. Therefore one teaspoon is equivalent to three reaspoons of good grade cod liver oil. Improved flavor and minimum cost to patient. For vitamin D slone (for the prevention or cure of rickets) we offer Smare Vitamin D a highly potent extract of the antischitic principle of cod liver oil prepared by methods (Zucker process) developed at Columbia University. Ten drops equivalent in vitamin D potency to three teaspoons of good grade cod liver oil.

S M A. CORPORATION "World's Largest

CLEVELAND, OHIO Producer of Carotene"



DOESN'T it give you a "kick" to be more than just "doctor" to

those young patients who are supposed to put physicians and the Spanish Inquisition in the same classification?

And aren't they a lot easier to treat successfully when they consider you a "regular fellow"?

Many physicians tell us that Ralston Wheat Cereal contributes materially in building up this "regular fellow" attitude on the

part of children—es pecially in cases of anorexia For Ralston, with its extra vitamin B, not only promotes normal appetites, but really tastes delicious Naturally those child patients are glad to think you've hunted high and low for their special benefit to find something that's not only good for them but good to eat, too

Value — Double
Rich in Vitamin B

Ralston Wheat Cereal is made of whole wheat (with only the coarser bran layer removed) Naturally rich in vitamin B—Ralston has been made double-rich by the addition of an extra quantity of wheat hearts Ralston, with its abundance of the highly nutritious body-building elements, contains more vitamin B than any other cereal for growing children.

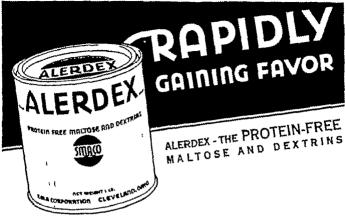
A Research Report on the new "doublerich" Ralston Wheat Cereal—and samples

for testing—will be sent to you FREE Use the coupon

RALSTON PURINA COMPANY, Dept. I, 150 Checkerboard Square, St. Louis, Mo. Please send me copy of your Research Report on the new Ralston Wheat Cereal and samples for testing

Name

Address
This offer limited to residents of the U S



## WHY IS ALERDEX PROTEIN-FREE?

• Since certain proteins are frequently the cause of ecremas and other forms of allergy it is desirable to chiminate these offending proteins from the infant diet Cereal proteins are frequently present as contaminants in some milk modifiers. The routine use of a protein free carbohydrate in all milk modifications should help to diminish the incidence of these troublesome eczemas. Alerdex is a protein free carbohydrate developed by our Research Division to meet this need and the demand for it is steadily increasing.

A modest announcement of Alerdex a year ago found physicians ready and anxious for such a product. There is now a definite trend to use Alerdex routinely in all milk formulas.

Of course Alerdex should slways be used as the carbohydrate addition with Smaco Hypo-Allergic Milks with the assurance that eczemas due to cereal protein sensitization will not be aggravated

#### CHARACTERISTICS OF ALERDEX

- Helps prevent eczames when used rout inely due to absence of offending protein.
- Use present formulae because Alerdex has same caloric value and percentage of meltors and dextrins.
- 3 Dees not cake on exposure to air because it is non-hygroscopic.
- A Disselves readily in warm water or milk.
- 5 Snew white, free flowing powder
- Inexpensive—in spits of extra processing under technical control, costs no more.
- 🖏 1822, B.H.A. Corporation, Clarestoni, Clin

#### APPROXIMATE ANALYSIS OF ALERDEX

Alard is essentially a mixture of approximately equal parts of maltose and dextrine his prepayed by a new tearmailty-controlled process of the ensymie hydrolysis of non-certal starsh, as a result of which it contains no record representation.

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Moletu e	3 0
Asb	2,0
Pat (cther atr ct)	0,0
Hed olesed protein (N g 5.25)	9 65
Reducing one re as maltosa	50,0
Destring (by difference)	40.6
Level tablespoons per sunce	4
Calett a ps level t bleapoon	2736
Caloriva per pauce	118



Prescribe Alerday in your own practice for samples and literature simply attects this paragraph to your letterhees a prescription blank. R.M.A. Corporation 4844 Prospect Avenue Clerains Ohie 56-123

UPON . THE . ASSIMILATION . OF

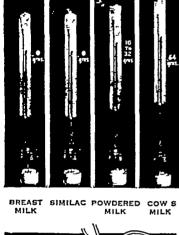
# FATS

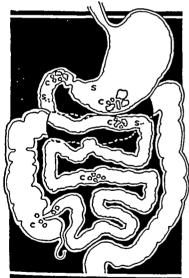
AT has a caloric value more than twice that of either carbohydrates or protein and serves very well to make up the necessary energy or caloric requirement. Two of the important vitamins, 'A' and 'D', are associated with the fat of milk and when the diet is low in milk fat these vitamins must be supplied in some other form "1

"When milk curdles in the infant's stomach it entangles a large proportion of the milk fat in its meshes and only such fat as hes near the surface of the curd can be reached by the digestive juices The amount of fat in the curd depends upon the amount of fat in the milk."3

The soft, fine curds of SIMILAC, which register zero on the tensiometer, expose a greater surface area for the digestion of the fat than do the large, tough curds of fresh cow's milk

The finer the curd the greater the surface The greater the surface area the more exposed are the fats, carbohydrates, proteins and salts to the digestive enzymes a more complete utilization of the food elements





C—Cows milk S—Similac Schematic drawing of the relative size of the curds of cows milk and Similac vom ited by six weeks old puppies after one half hours ingestion.

<sup>1</sup>Marriott Infant Nutrition, pg 49

Morse and Talbot, Diseases of Nutrition and In 3 Talbot fant feeding, pg 48

Samples and literature will be sent on receipt of your prescription blank.

SIMILAC—Blade from fresh skim milk (casein modified) with added lactose salts milk fat and vegetable and cod liver oils



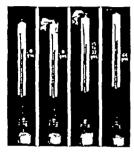
DIETETIC

ABORATORIES, INC.,

## CURD TENSION - AND INFANT FEEDING -

EFFECT UPON THE ASSIMILATION OF

## CARBOHYDRATES



ITS

BREAST SIMILAC POWDERED COW'S MILK MILK MILK



C.—Cow milk 5.—Studies Schematic drawing of the relative size of the curds of cow's milk and Stralles vented by rix weeks old pupples after onehalf bear's insertion.

HE curds of milk contain only a small amount of carbohydrates, sufficient, however, to be a disturbing factor in infant feeding.

"A large part of the digestion and absorption of the carbohydrates takes place in the upper part of the small intestines."

"The disaccharides, maltose, sucrose and lactose, are converted into monoaccharides through the action of enzymes secreted by the small intestine and are absorbed in the form of monoaccharides.

"When absorption is impaired, some sugar may reach the large intestine and here be attacked by the bacteria present. Sugar itself rarely appears in the stool, it being decomposed to form neids and gases."

The large, tough curds of cows milk are more slowly disintegrated and thus more slowly release the encased carbohydrates than the soft, floeculent curds of SIMILAC.

The disintegration of the curd of cow's milk may not be completed until after the curd, with the encased earborhydrate, has paused that portion of the small intestine when the ensymes for the conversion of disacharides into monoseccharides are present. There is not this possibility when SDIRAC is fed because the fineness of the curd of SIMILAC does not permit of the encasement of carbohydrates to any extent.

The finer the curd the greater the surface area. The greater the surface area the more exposed are the fats, carbohydrates, proteins and salts to the digestive enzymes. Result a more complete utilization of the food elements.

Landan & Palayzova Zeitecke f physial, Chem. 1906, XLIX, 128. Marriett: Infent Spirition, pg 81.

Samples and literature will be sent on receipt of your prescription blank.

SIMILAC-Med from fresh skim milk (casein modified); with added lactore salts milk f t and vegetable and cod liver oils



DIETETIC

M& K LABORATORIES, INC.,



NOTE the eagerness with which babies eat Clapp's Original Baby Soups and Vegetables

Then you'll agree with us that Clapp foods, rich in bone and body building properties, are packed full of appetite appeal for babies

Clapp products in the new Enamel Purnty Pach (the purest packing foods can receive) are now selling at a new low Price of 15c You can now freely advise these infants a varied diet

save money for their parent

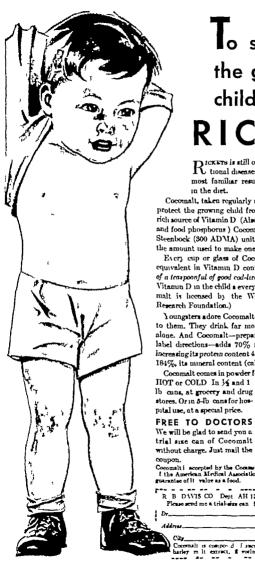
Send for free booklet, "Strained Vegetable Infant Feeding " Address Harold H Ca Inc., Dept J.9, 1328 University in Rochester, N Y

## 15 VARIETIES

Baby Soup (Strained) strained) Vegetable Soup Beef Bret Wheatheart Cereal Carrots $P_{eas}$ 14 Tomatoes Backs Beans

Prune Pulp  $P_{ulp}$ Apple Sauce.

Clapp's original Baby Soups and Vegetables · · also packed in glass Jars at former prices



## To safeguard the growing child against RICKETS

Rickers is still one of the most common nutri most familiar results of a lack of Vitamin D in the diet.

Cocomalt, taken regularly instead of plain milk, helps to protect the growing child from nickets for Cocomalt is a rich source of Vitamin D (Also a rich source of food-calcium and food phosphorus ) Cocomait contains not less than 50 Steenbock (300 ADMA) units of Vitamin D per ouncethe amount used to make one drink.

Every cup or glass of Cocomalt, properly prepared is equivalent in Vitamin D content to not less than one-half of a teaspoonful of good cod-later oil. The value of this extra Vitamin D in the child a every-day diet is apparent. (Cocomalt is beensed by the Wisconsin University Alumni Research Foundation.)

Youngsters adore Cocomalt—it s a chocolate flavor treat to them. They drink far more than they would of milk alone. And Cocomalt-prepared according to the simple label directions-adds 70% more calone value to milk, increasing its protein content 45%, its carboby drate content 184%, its mineral content (calcium and phosphorus) 48%.

Cocomalt comes in powder form, easy to mix with milk-HOT or COLD In 1/2 and 1 lb cans, at grocery and drug

pital use, at a special price. FREE TO DOCTORS

We will be glad to send you a trial sixe can of Cocomalt without charge. Just mail the

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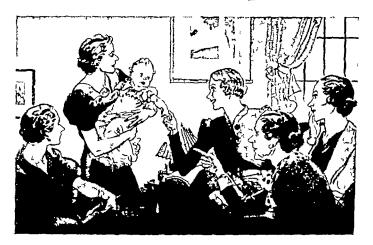
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of Balyent Hay Fever and Asthma Clinic Oklahoma City Okla

A short comprehensive discussion is given concerning the rôle played by foods in asthma hay fever migratine, utricaria and certain types of eczema and gesturo-intestinal symptoms. Breeife food sensitization in relation to vertigo, onliepsy, arthritis, pruritus and bladder irritation is also discussed. Methods of testing for protein sensitization are described.

## MIGRAINE

Diagnosis and Treatment

By RAY M BALYEAT M.D asoc. Prof Medicine and Lecturer on Diseases Due to Allergy Oklahoma.

This book covers the definition of migraine and historic consideration the hereditary factor incidence etiology symptomatol ogy pathology laboratory data and prog nosis treatment of nonsitergic and allergic nosse treatment of nonstressic and shedfoly of migraine the localization and specificity of cellular sensitization clinical records in proven cases of allergic headache illustrat ing methods of diagnosis of migraine from other allergic headache, and treatment.

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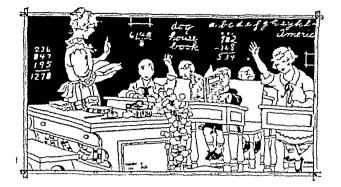
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## Synopsis of Baby Shoe Research

Under this title the Department of Medical Co-operation of Mrs Day's Ideal Baby Shoe Company has collected the results of its own extensive studies of this important subject Included, also, is other material not readily available elsewhere, all arranged in convenient form for ready reference

This Portfolio is offered to the profession to aid in the efforts to promote foot health and to prevent improper foot development

As a result of its research, supervised by orthopedic specialists, this company developed certain fundamental principles of design and construction which are followed in the making of Ideal Baby Shoes All are fully described in the Portfolio which will be sent to any member of the profession who requests it on letterhead or prescription blank Address

Department of Medical Co-operation

MRS DAY'S IDEAL BABY SHOE COMPANY

DANVERS MASS.

## THE Importance of Vitamins IN THE DIETARY

THE increasing recognition of the importance of vitamine in the dietary together with dis coveries of hitherto unknown functions of these mysterious food components has focused undue attention upon specific vitamins and less upon others of equal importance. It is but natural that those sponsoring a product having a high potency of any single vitamin should stress the

value of that one above all others.

But medical research has demonstrated that it is becoming increasingly difficult to separate definitely the functions of one vitamin from those of another For example investigation appears to show that vitamin D associated with calcium and phosphorus tends to prevent dental caries. It also appears that vitamin C is likevise of value in the prevention of tooth decay. It has been shown that an excess of vitamin D increases the tendency to infection unless the ingestion of vitamin A is correspond Ingly increased Research has indicated that not only vitamin A but also vitamins B and G are growth promoting. In a word the sym pathetic unity of action of vitamins must have the physician's careful consideration

Further it has been shown that there exists a definite balance between vitamins by greatly increasing vitamins A and D in diets, an other wise adequate amount of vitamin B is made inadequate-leading to death of animals. Care should be taken not to overdose with cod liver oil or viosterol unless, at the same time an in creasing quantity of vitamin B and G are also added to the diet. As a result of new informa tion, there is a growing tendency on the part

tion, there is a growing tendency on the part of the medical profession to advocate the administration of vitamins in group form.

Maltine With Cod Liver Oil provides a generous amount of four ystamins—A B D and G in one palatable nutritive combination 70%. is Maltine, a concentrated extract of the nour ishing elements of malted barley wheat and oats—rich sources of vitamins B and G 30% is pure, vitamin-tested cod liver oil—of high potency in vitamins A and D Taken with orange or tomato juice vitamin C is added Maltine With Cod Liver Oil is biologically standardized and guaranteed to contain vitamins A, B D and G Biological and vitamin report on request. The Maltine Company Established 1875 30 Vesey Street, New York N Y

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Every baby is a special baby. baby's digestive ability as Every baby is, therefore, an well as its most urgent needs

which your own prescription alone can solve. Your own formula—based on the condition of the infant—one that

individual feeding problem is the best assurance of suc-

cess in infant feeding. KLIM is a safe, pure, uniform milk, easily digested and assimilated and readily adaptable to

takes into consideration the your prescriptions.

AUTHORITY As the doctor says the multi-plication of complicated foods through the in terests which push them for commercial reasons is out of proportion to their value For the general practitioner to adapt the formula to abnormal conditions from a printed card is difficult. Since the compound is fixed it is

impossible to vary the amount of a single in gredient without varying the amount of all the other contained ingredients by the u e of either dilution or concentration. Scientific medication with shot gun' prescriptions is no more impossible than scientific feeding with shot gun proprietary infant foods

(Dr. Henry E Irish discussion of Dennett's paper The Teaching of Infant Feeding Arch Pediat Vol VLVIII No 4 April 1931)

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## Warn mothers against forcing the



child to eat

Loss of appetite, under-weight may often be overcome by giving chil dren a daily addition of Vitamin B

Mothers are alarmed when the child stops eating and falls to gain weight. They may know it isn't wise to 'baby' or

scold But they would rather risk spoiling

the child than to endanger her health.

Often a word from the physician helps solve the problem. The physician may discover that the childs trying behavior has resulted directly from a period when her diet supplied very little of the factor essential for good appetite—Vitamin B

All children need this factor Their appetite is almost sure to be affected when they do not get enough. And the diet of many children consists largely of refined cereals milk and foods which are not especially rich in Vitamin B but contains few fresh fruits and vegetables which are good sources of the vitamin.

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It increases by many times the Vitamin B value of milk. Three heaping teaspoon fuls added to a glass of milk raise the Vita min B content to that of a whole quart.

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Have mothers give this drink with meals or after school every day It is deliciously flavored Children like to drink it.

For better appetite and increased weight when the child's diet contains insufficient Vitamin B-Squibb's Chocolate flavored Vitavose!

F Infants—Suggest Squibb a regular Vitavosa or Dextro-Vitavosa Milk-modifiers for bables who need extra Vitamin B Prescribe Dextro-Vitavos I r the newly born, Vitavosa for older bables.



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## The Journal of Pediatrics

Vot III

DECEMBER 1933

No (

## Original Communications

#### THE TREATMENT OF CHOREA BY INDUCED FEVER

LUCY PORTER SUTTON, M.D., AND KATHERINE G. DODGE, M.D. NEW YORK, N. Y.

SINCE October 1930, most of the cases of chorea admitted to the Children's Medical Service of Bellevic Hospital have been treated with fever produced by the intravenous injection of typhoid paratyphoid vaccine. We report in this paper on the results obtained in 150 cases and offer a comparison in 150 cases cared for on the same service prior to 1930. A preliminary report on the first 24 cases so treated was published in 1931.

The volume of literature written about chorea is tremendous and is evidence of the lack of knowledge other than clinical about the disease Neither the pathology nor the bacteriology is definitely established. The general opinion is that chorea is an encephalitis involving the basal ganglia and that it is due to the same toxic agent as that which causes rheumatic fever. The number of different treatments used for chorea makes a long list. With certain exceptions none have appreciably short ened the course of the disease.

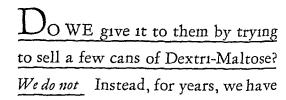
In 1923 Theor von Kern's reported three children with chorea to whom he gave intramuscular injections of milk at three to five-day intervals. He felt that the course of the attacks had been shortened to three or four weeks' duration but did not attribute the results to the fever produced. Several other reports occur in the German hierature on this method of treatment. In 1927 I Somogya' published in an Hungarian periodical the results obtained in 30 cases. He felt that the course of the attacks was shortened to from three to five weeks. He gave the injections in the clinic and allowed the patients to go home to have the reaction. The authors who reported on the use of milk injections discussed the mechan

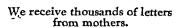
From the Department of Pediatries New York University and the Children's Medical Service of Bellevue Hospital
This work has been done with the help of a grant from the Josiah Macy Jr.,
Foundation.

## When the Mothers of America

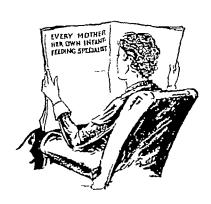
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Nowadays, the public is plagued with a vast amount of gratuitous, meddle some, medical advice.



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## The Journal of Pediatrics

Vot. III

DECEMBER, 1933

No 6

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From the Department of Pediatrics New York University and the Children's edical Service of Relievue Hospital. This work has been done with the help of a grant from the Josiah Macy Jr. Pounlation

nism of the foreign protein reaction and apparently did not consider the possibility that fever might be the effective factor

In 1929, Roeder first reported on the use of mrvanol (phenyl-ethylhydantom) in chorea, and since then many articles have been published. most of them reporting on rather small series of cases course of an attack of chorea is definitely shortened by the use of the drug, at least in those cases which show fever as a result of the drug In a very reasonable article on this subject Pilcher and Gerstenberger<sup>5</sup> state that the majority of patients who react to the diug with fever and morbilliform rash usually improve rapidly, while milder cases and those who do not react with fever and rash are not appreciably A few recent reports have commented unfavorably on this treatment, in that the authors failed to see beneficial results from the use of the drug Here again the actual number of cases is small

The danger of nirvanol lies in the poisoning which may result in serious complications and even death. Some such cases have been reported in the literature, and we have been told of others not reported The complications may be nephritis, pneumonia, hyperpyrexia, or extensive and intractable skin lesions. On the other hand, Dennett and Wetchler have reported a series of 72 cases of chorea treated with nirvanol with no serious complications whatever They feel that the drug can be given safely to children in the hospital and under competent medical supervision

In 1930 Mas de Ayala" s reported the case of a child with choica to whom he gave relapsing fever. The result was very striking, and after the fourth bout of fever the improvement was complete This author claims to have been the first to use fever therapy in chorea appeared in the Spanish literature and was not found by us until some time after it had been published. Also, we, as well as others, have observed the beneficial effect of an intercurrent acute februle illness such as measles, typhoid, acute tonsillitis, on chorea

Dr Nathaniel Chapman in 1818\* said "The intermittents do some times cure other diseases, as gout, rheumatism, acute and chronic, chronic cutaneous eruptions are frequently cured by them, spasmodic complaints as chorea, epilepsy, asthma, hysteria, mania and especially melancholia I have told you it is the fashion in Europe to send patients with pulmonic complaints to miasmatic countries, and you have heard of the practice being used in our own country"

<sup>\*</sup>Dr Richard Kern of Philadelphia in a personal communication gives the source of this quotation as follows

There are in existence two large notebooks written apparently by an auditor of Dr Chapman's lectures as delivered in the University of Pennsylvan's School of Medicine in the year 1818 These notebooks are in longhand and are practically identical suggesting that the writer was an individual who took down Dr Chapman's lectures possibly stenographically and sold the copies to medical students.

The copy which I was able to see several years ago is one that was in the hands of a medical student who was at the University at that time and has come down to one of his descendants Dr David L Farley of our Medical Staff

The other copy is in the possession of the Dean of the Medical School Dr William Pepper

Since the one factor common to treatment by milk injections, nirvanol intoxication, relapsing fever intercurrent infections, and typhoid para typhoid vaccine injections is the production of fever, it is difficult to escape the conclusion that it is the fever which is beneficial in chorea, rather than the instrument which produces fever

We first started to investigate the use of fever therapy in chorea in 1929 In March of that year a boy with severe chorea was given luminal as a sedative He became intoxicated with the drug and developed a high fever To our surprise the chorea began to clear rapidly after a few days of fever The symptoms which this boy exhibited were similar to those which occur in nirvanol poisoning, namely rash and fever Since luminal had been used by us before in chorea with no beneficial effect on the disease, it seemed logical to investigate the matter of fever therapy For about a year we tried to produce fever with typhoid vaccine intravenously but found it impossible to get continuously satis factory fever with this vaccine However, an occasional good febrile result occurred followed by apparent improvement in the chorea, so that we were encouraged to continue the investigation. Finally in the fall of 1930 we began to use typhoid paratyphoid vaccine, and found that we could produce fever almost at will The reason that typhoid vaccine and later typhoid paratyphoid vaccine were chosen as the means of pro ducing fever was that it is cheap, easily available requires no elaborate set up and is safe Malaria was considered, but only luctic blood was available at that time There is also a definite mortality among pareties from the maleria itself

A method of procedure has been developed which produces satisfactory results. It should always be kept in mind that the object of the treatment is to shorten the attack by producing fever of at least 104. F and that the vaccine is merely the means of obtaining the fever. We have found that a temperature of less than 104° F is of little use and feel that a fever of between 104° F and 100° F is the most effective

Treatment with intravenous triple typhoid vaccinet Aims

<sup>1</sup> To shorten the duration of the chorca, and therefore treatment is begun as soon after admission as possible.

<sup>2.</sup> To get a daily temperature rues of 104 or over and to maintain it for as many hours as possible. Treatment being given daily until all signs of chorea have obsared. A day when the temperature does not reach 104 is a wasted day!

<sup>3.</sup> To make the children as comfortable as they can be made during treatment Method

Use New York City triple typhoid vaccine (containing 1000 million B typhorus 750 million each of Para A and B per c.c.) a tuberculin syringe, and 24 G % needle.

<sup>2.</sup> The vaccine should be boiled for three minutes before the first time it is used, and always kept in the ice box between treatments.

instructions developed for use of the internes on the Children's Medical Service at Bellevue Hospital

- 3 First dose 0.05 cc TTV, undiluted, intravenously
- 4 Second dose is governed by the reaction of the child to the first dose for instance if the temperature the first day goes to  $106^\circ$  or over, repeat 0.05 c.c. the second day it it goes to  $105^\circ\pm$  then give 0.075 c.c., and if to only about  $104^\circ$  then give 0.1 c.c. TTV
- 5 Subsequent doses are determined entirely by the reaction of the child. In general increase the dose of vaccine by a larger amount each day. The average case may take first day, 005 cc, second day, 0075 c.c., third day, 015 cc, fourth day, 025 c.c., fifth day, 04 c.c., sixth day, 06 cc., seventh day, 085 c.c

However, this routine cannot be counted on to obtain adequate temperature elevation. A much larger increase may be necessary or

6 Second doses on the same day may have to be given If the temperature does not reach 103°, or only one or two readings in the neighborhood of 103° are obtained, then a second dose on the same day should be given. This second dose is usually one-third to one half the original dose of the day. For instance if the first dose of the day was 0 6 cc and at the end of two hours the temperature is 103 2° and fifteen minutes later is 102 8°, then 0 2 cc TTV should be given at this time If the temperature has dropped below 102°, then 0 3 c.c should be given

Note In giving the second dose it is necessary to get it in as soon as possible after the temperature becomes stationary or begins to fall, otherwise a temperature

curve like this \_\_\_\_\_\_ instead of like this \_\_\_\_\_\_ e be obtained When it be

comes obvious that a second dose may be necessary, have temperatures taken more frequently than one q hour, so that it will be known almost as soon as it begins to fall

- 7 Keep the child well covered during the whole of temperature reaction If the child becomes uncovered, temperatures do not stay up so well
- S Treatment should be given daily unless condition of patient indicates need of a rest (severe vomiting, poor fluid intake, etc.) or unless the ward situation makes it impossible. Never give first dose on a visiting day. (The child may be taken out by the parents with a temperature of 104° if you do.)
- 9 Treatment should be given until all signs of chorea have disappeared. This is generally easy to tell in the mild and moderate cases, but may be more difficult in the severe ones. If there is much weakness and pseudoparesis present, there may be incoordination due to this weakness and to the prolonged treatment, after all signs of true chorea have cleared. When in doubt try massage and occupational therapy The mild and moderate cases take on an average of 5.7 treatments and the severe cases 10.15
- 10 Urines should be examined by the interne daily during treatment, for albumin and red cells. In our series we have not seen anything more than a transient albuminum, and occasional red cells. However, hematum has been reported to us. Therefore if the urine shows more than an occasional red cell, stop treatment until the hematum clears.
- 11 Occasionally, especially in severe cases, a second course of vaccine may be necessary after an interval of several days or longer. In this case we have found that the size of the first dose of the second series depends on the interval. The following is a rough guide for dosage.

Interval of 13 days-Proceed as though there had been no interval.

Interval of 47 days—Give the same dose as that given on the last day of the first series

Interval of 8.9 days— It is probably best to give a somewhat smaller dose than that given at the end of the first series, although if the reaction to that dose was poor, then the same dose may be repeated

Interval of 10 20 days—We have had no patients who have fallen into this group. To be safe the dose should probably be decreased to about one-half the previous dose at 14 days and to one-quarter at 16 days.

Interval of 20 days -Series should be started over again at 01 c.c.

Care of patient during reaction

- Protein shock, with chill, severe headache, vomiting etc., generally occurs 20-50 minutes after the vaccine is given. The children are more comfortable if already hot, therefore extra blankets and hot water bottles should be given as soon as the vaccine has been given.
- 2 Codence in maximum doses (14 to 5, gr according to size of patient) reheres the headache to some extent. This should be given about 20 minutes after the vaccine on the first and second days of treatment, and should be given by hypodermic in thigh (to avoid a sore arm on which a tourniquet will be put the next day) After the first two days' treatment the codeine may not be necessary and it may therefore be left as an S O S order, which may be given by mouth if the child is not vomiting
- 3. Vomiting usually occurs during the first two or three reactions. Therefore lunch is omitted on these days. After this, vaccine may be given immediately after the noon meal. If for any reason the vaccine is to be given at another time during the day, see that provision is made for adequate food intake at some time during the day.
- 4 We have found that large drinks of fluids are likely to bring the temperature precipitously down and therefore fluids should be limited during treatment. Small sips of water or fruit juice however make the children much more comfortable Treatment of hyperpyrexia.
- 1 Aspirin gr 5 ice-cap to head and a drink of water are usually given if two readings above 106 at fifteen minute intervals are obtained. This should be done routinely if there is no doctor on the ward. However some of the children have surprisingly little discomfort at high temperatures, and unless the temperature is going dangerously high, these procedures may be omitted, if the interne is present to assume responsibility for it.
- 2 For very high temperatures 107 or more all coverings should be taken off immediately and the child given a tepid sponge. Aspirin gr 10 should be given by mouth unless the patient is vomiting or is unconscious in which case give a double does 15 20 gr by rectum. Take the temperature every ten or fifteen minutes. If it continues to go up the child may be placed in a tub of water at 100, the water then being gradually cooled. Sedatives and stimulants should be given as indicated.

Note These very high temperatures seldom occur, and when they do usually they respond readily to the above treatment. They are not so terrifying as they look! Routine orders usually written on the chart

Vaccine given at 12 r ii Take the temperature stat, and q 1 hr until it returns to 99 6 (q 14 hr when above 104 on the way up)

Extra blankets and hot water bottles stat.

Codeine gr 1/2 (h. in thigh) at 12 20 and repeat after hrs. 3 if necessary

Limit fluids to small sips of water lemon or orange juice.

Aspirin or 5 and ice-cap to head for temperature over 106

Daily urine to laboratory during treatment

Do not be afraid of high temperatures—they are necessary to cure the choren Do not be afraid of large doses of vaccine

Care of the patient during convalescence

 Children are kept in bed at least one week after completion of fever therapy longer if the chorea has been severe or if there has been any evidence of active earditis.

- 2 High caloric diet to make up for the loss in weight which usually occurs during treatment
  - 3 Occupational therapy (basket weaving, coarse sewing, etc.)
  - 4 Transfusion if indicated for anemia
- $5\,$  Children are sent to a convalescent home from the hospital if possible Treatment of subsequent attacks by TTV

There is apparently no increased sensitivity to the vaccine. In general we have found that more vaccine is required to obtain the desired temperature reaction when a child is being treated a second time with vaccine, than was required during the first course of treatment

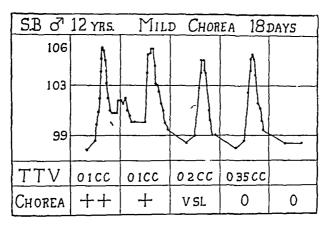


Fig 1—S B Mild chorea—first attack Shows (1) good temperature reactions with small doses of vaccine (2) secondary rise on first day of treatment which occurs in about 50 per cent of the cases (3) good response to short course of treatment

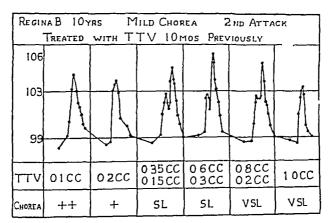


Fig 2—R. B Mild choren—second attack Pirst attack treated with T T V ten months previously Shows (1) relatively larger doses of vaccine necessary (2) second doses on same day (3) longer course necessary in a second attack

The average number of treatments in the 150 cases reported here was 6.24. In the mild cases the average was 5.14 treatments, in the moderate 6.47 and in the severe cases 8.88. The minimum number of treatments was 3, the maximum 18.

In some children, particularly the severe cases where there has been marked hypotonia, it may be difficult to decide just when the incoordina tions are due simply to weakness rather than to chorea. In these cases massage and occupational therapy are given. If the weakness decreases with increased activity, we feel safe in saying the attack is over. If the

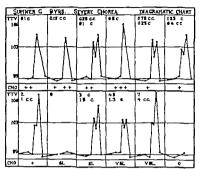


Fig. 3.—G. Sewers choren of two weeks duration. (Case treated at The Nursery and Childs Hospital, countery of Dr. Louis Schreder) Shows (1) sewer chores responding readily to vigorous treatment (2) good temperature reactions (3) large doses of vaccine necessary.

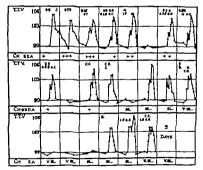


Fig 4—S. R. Severe chorea of one month's duration. Shows (1) case difficult to cure, requiring long course of treatment (2) relatively poor temperature reactions (3) relative of chorea, on rest after thirteen treatments.

incoordination becomes worse, it denotes continued activity of the disease and treatment is resumed. In the ordinary moderately severe or mild case there is usually little difficulty in knowing when the attack has been arrested

The types of febrile reaction obtained by this method are shown in Figs. 1-4

While the majority of cases respond readily to fever therapy, a certain small proportion are disappointing in their results. Fig. 4 shows a case of this sort, in which, although the choica improved from severe to very mild in a reasonable length of time, i.e. ten days, definite choreform movements persisted for more than two weeks longer. In general

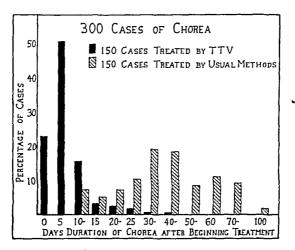


Fig 5-Duration of the choren after beginning of treatment in 300 cases

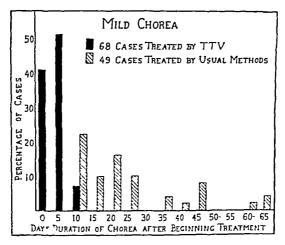


Fig 6-Duration of the choica after beginning of treatment in 117 mild cases

these difficult cases are likely to be repeaters, or cases in which the duration of the present attack has been long before treatment was begun. While most of these difficult cases fall in the severe group, an occasional one is found in the moderate and even in the mild group. In this litter group it is particularly difficult at times to determine how much if any of the residual movements is due to frue choica, and how much to habit. Of 150 treated cases, only 10 per cent responded to

treatment in this way. The longer the course of treatment the more difficult it becomes to obtain adequate febrile reactions, and this fact increases the difficulty in treating some of the more severe cases. In general, the results are prompter and more complete in cases treated early in their first attack.

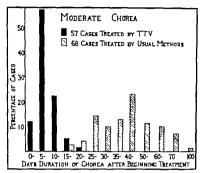
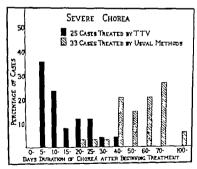


Fig. 7 - Duration of the chorea after beginning of treatment in 1 5 moderate cases.



Pig. 8 -Duration of the chorea after beginning of treatment in 58 severe cases.

The advantages of the typhoid paratyphoid vaccine method of producing fever are that it is cheap safe simple, and produces the desired therapeutic result. The fever follows immediately after the injection, in contrast to the one to two weeks' interval which must clapse before the toxic effects of nirvanol appear.

Because we thought that a temperature maintained at a high level for four or five hours might be more effective than the type of fever obtained with vaccine alone, and thus necessitate fewer treatments, we tried using a combination of vaccine plus blanket packs in a number of cases. We found that we could maintain the fever for several hours, and got temperature curves similar to those obtained by the radiotherm and diathermy methods. However, the children were more exhausted the following day than when vaccine alone was used. A day without treatment was therefore often necessary, and time was lost. We finally discontinued this method because of the following case.

A P, a girl twelve venus old, was admitted in her third very severe attack of choren We had treated her second attack a year before with a very good result. Treatment was started as usual, and she showed marked improvement The fourth dose of vaccine was given at 8 30 one morning. Her temperature reached a maximum of 101°, and then dropped until at 3 30 it was 100° by rectum. In other words she had almost no reaction to the vaccine, and it was all over by mid afternoon Because of the poor febrile response to the vaccine she was blanketed about 3 30 Her temperature rose slowly to 1028° at 6 P M, and she was in good condi The nurse went back to her fifteen minutes later and found that her tem perature was 1098° and that she was unconscious The resident and internes immediately took measures to reduce the fever and it came down to 101° within three hours At 11 30 PM she began to have convulsions which lasted several hours. the temperature rose to 103° the next morning and she died in the afternoon Autopsy showed massive lobular pneumonia of both lungs, early vegetative endo carditis of the mitral valve, which had not been sufficient to produce physical signs, and microscopic evidence of past inflammation of the aortic valve pneumonia had been caused by the means taken to reduce the temperature we cannot say, it was not suspected before the child was put in the pack

Study of the brain by Dr Lewis Stevenson showed

"A longitudinal section through basal ganglia shows very many distended blood vessels. In the lenticular nucleus and caudate nucleus there are also very many distended blood vessels and to some extent in the posterolateral part of the optic thalamus. Apparently, this is true of the optic radiations as well. There is apparently a slight amount of hemorrhage in the posterior horn of the lateral ventricle, straining the ependyma. In the left hemisphere these distended vessels appear in the internal and external capsules and again in the optic radiation and to some extent in the optic thalamus near the internal capsule.

"Microscopic Examination of Brain—Microscopic sections of caudate nucleus, lenticular nucleus show a mild degree of encephalitis evidenced by small round celled infiltration about some of the smaller vessels. Section of different parts of cortex failed to show this reaction, there is no evidence of meningitis."

This case demonstrated entirely too well what we already knew, namely, that the temperature can use very high and very rapidly from the use of packs, which cause fever by preventing loss of body heat by radiation. It is important to realize that this fatality was not caused by the vaccine. This is the only death in our series of treated cases.

On the other hand two other children whose temperatures went over 109° from the packs sustained no ill effect, and the beneficial effect on the chorea was definite. The highest temperature from vaccine alone was 108° and this occurred in only one case.

#### RESTIL/IS

The results with fever therapy in chorea seem to us rather striking We have made no attempt to run a control series, since this would involve subdivision of cases into groups according to age, sex, number of attacks, duration and severity of attack, and season of the year. This would necessitate a very large number of cases. Moreover, it has been known ever since Sydenham first described chorea that the duration is prolonged, that the average attack lasts six to ten weeks, and that even a mild case may last for months.

For comparison with our results, however, we have gone back over the records of children with chorea treated in Bellevue between 1920 and 1930. We found 150 records with sufficiently detailed and frequent progress notes to determine the actual duration of the chorea in the

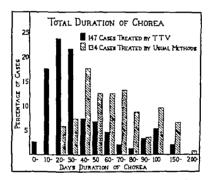


Fig 9—Total duration of the chorea in 181 cases. This includes, in the treated group duration before admission plus observation period plus duration of movements after beginning of treatment in the untrented group duration before admission plus duration in the hospital.

hospital The treatment given these children included Fowler's solution sodium salicy late calcium lactate thyroid extract, high caloric diet starvation, hot and cold packs, hydrotherapy autoserum therapy rest, catharsis bromides, luminal, and other sedatives

The cases in both the comparative and the treated series have been grouped as mild moderate and severe. In the comparative group there are a number of children who were admitted as mild cases which became moderate and others admitted as moderate which became severe. These were put into the moderate and severe groups respectively.

The mild group consists of cases of undersable chorea, but with little functional incapacity. The moderate group includes the cases with continuous, incoordinate movements, with some speech impairment. Such children have difficulty in performing voluntary acts, and the gait

is that of a drunken person, they can run better than they can walk The severe group is composed of those with marked hypotonia, and pseudoparesis. The hypotonia may be so great as to mask the choresform movements. These children are unable to speak intelligibly, have difficulty in chewing and in swallowing even liquid food. They have no control whatever over their movements or emotions, and may be unable to try to perform voluntary acts.

The duration of the choica in the hospital in the group used for comparison, and the duration in days after beginning of fever treatment is shown in Table I

TABLE I

TIPE	\UMBER OF CASES	AVERAGE DURATION IN DAYS	RANGE IN DAYS
MILD			
Comparative group	48	27 4	10 67
Treated group	68	5 72	2 14
MODERATE			
Comparative group	68	44	15 120
Treated group	57	8 56	3 22
SLVERE			
Comparative group	33	62 4	24 180
Treated group	25	158	5 47
WHOLE SERIES			
Comparative group	150	42 6	10 180
Treated group	150	8 5	2 47

A comparison of the two groups confirms the impression that the cases of chorea at Bellevue treated by means other than fever had a considerably longer duration than those treated by induced fever. Figs 5 to 9 show this graphically

The question arises whether a somewhat herore treatment is justified in a disease which in itself is iaiely fatal. We feel that it is for the following reasons. It reduces the time spent in the hospital and hence cuts down the expense to the institution. It lessens the period of time lost from school by the child Although considerable nursing care is required during the treatment period, the nurses are relieved of the prolonged care of an untreated case. The mental agony endured by a person with choica seems to be great. Several older children who have been treated in well-advanced attacks have come back to us saving that they felt an attack coming, even before we ourselves could have been sure of the diagnosis, and would we "please give them the needles right away,' so they could get back to school and not have a A sixteen-year-old boy who had had two prolonged at tacks was recently treated in his third attack on the adult service at Bellevue Hospital When asked what he would do if he got a fourth ittack, his reply was, I'd come back for more needles" This is the reaction of those who have had treated and untreated attacks, and seems to us justification for the treatment

Of the 150 patients with treated attacks reported here 28 patients already had organic rheumatic heart disease. None of these children were harmed in any way by the treatment. Dight children who had definite evidence of active carditis at the time treatment was started, had lost the signs of activity by the time the treatment of the chorea was over. We feel therefore, that the presence of either active or mactive heart disease is not necessarily a contraindication to treatment. We would hesitate to give the treatment in the presence of a very severe carditis as evidenced by a pericardial friction rub but fortunately this combination seldom occurs.

It has been gratifying to hear from physicians in various parts of the country that this method of treating chorea has been used satis factorily in about 100 other cases. We suspect that those who failed to get good results have probably not followed our technic, and have therefore not obtained good febrile reactions.

A chorea clinic has been established to follow these cases, and we intend to observe them for a period of at least five years from the time of treatment. There seems to be no rational basis for anticipating a reduction in the number of recurrences of chorea in these treated cases. However this question of recurrences as well as that of development of heart disease is being carefully watched and at the end of the observation period data on both treated and untreated cases will be available. So far we have had about 98 per cent follow up of cases. The number of recurrences is relatively small, but since the treatment has been in use only about two and one half years, and since chorea may recur after a lapse of a number of years, our present figures on recurrences have no final value.

Investigators are working continually to perfect methods of producing fever and will doubtless some day devise an apparatus which will be safe in ordinary hands and will lack the unpleasant features of foreign protein shock or of radiothermy and diathermy and which will at the same time be neither expensive nor elaborate. Until then intravenous injections of typhoid paratyphoid vaccine can be used as a fairly rehable and safe method of treating chorea.

### BUMMARY

Intravenous injections of typhoid paratyphoid vaccine as a means of inducing fever have been used in 150 attacks of chorea. Comparison of the duration of chorea in the hospital in 150 attacks treated by other methods show that the duration of the attacks has been reduced from an average of 274 days in the mild untreated cases to 572 in the mild treated cases from 44 days in the untreated moderate cases to 856 in the moderate treated cases and from 62.4 days in the severe

untreated cases to 158 days in the severe treated cases. We conclude, therefore, that fever therapy is a satisfactory method of treatment of chorea

We wish to express our great appreciation to Dr Charles Hendee Smith for his interest in this study and his very helpful encouragement

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## TILL TREATMENT OF PNEUMONIA IN INFANTS AND CHILDREN WITH ANTIPNEUMOCOCCUS SERUM

ROSA LEE NEMIR, M D NEW YORK, N Y

NTIPNEUMOCOCCUS serum has been used extensively in the treatment of pneumonia in adults. For some types the results have definitely proved its value in reducing the mortality rate purpose of this paper is to report the results of antipneumococcus serum therapy in the pneumonias of infants and children for similar types of pneumococci and for the more recently isolated types so frequently found in infants and children

Lobar pneumonia in children (two to twelve years) is notably a benign disease under two years, it approaches in severity the pneumonia of Bronchopneumonia is distinctly a very serious disease both in its course and in its mortality rate. For the past three years on the Children's Medical Service at Bellevue Hospital, the mortality rate of bronchopneumonia is approximately 60 per cent and of lobar pneumonia in infants under two years approximately 20 per cent. These figures re fer to pneumonias irrespective of etiologic agent. These percentages contrast sharply with a mortality rate of 5 per cent for lobar pneumonia in children over two for the same period of time on the same wards. On the other hand, the mortality rate of pneumonia in adults varies from approximately 20 per cent to 45 per cent, depending upon the type of infecting organism. Obviously other enteria than those used for adults must be employed in the evaluation of antipneumococcus serum therapy in infants and children. The criteria here used are the effect on the severity and progress of the disease as judged by the duration of the pullimonia and the effect on complications.

This study was begun in January, 1932, and included a clinical and bacteriologic observation of 868 patients with all types of pneumonia This report comprises 207 patients the remaining 161 are not included as they represent patients having pneumonia due to bacteria other than the pneumococci types for which we have specific serums. During this investigation therapeutic serum was available for the following types of pneumococci I II IV V, VI A and B VII XIV XVIII, XIX, and XXII New serums have been produced for other types since the begin ning of this study

From the Department of Podiatrics, New York University Medical School, and the Children's Medical Service, Believine Hospital, and the Research Laboratory of the Department of Health, New York City
This investigation was made possessible by a grant from the Commonwealth Fund to the New York University for research in pneumonia, It has seen conducted at the suggestion of and under the second of the Children of the Children Medical Service, Believing Spatial, for his criticisms and odvice. The bacteriologic typing was done under the supervision of Miss Julia Vinograd. Assistance was also given during the first year by the Altman Foundation.

four hours was from 6 to 9 c c for an infant and from 15 to 25 c c for a child One dose was usually given after the temperature had remained below 100° F for a period of from two to four hours Ficquently, three or four doses were sufficient and never were more than seven given. Intravenous administration of serium is so much more effective than the intramuscular method that the first one or two doses should be given intravenously, after this first dosage, serium may be given intramuscularly with good results

Serum Reactions—The amount of serum administered is usually too small to give serum sickness. Only one patient of the 82 treated developed this reaction. One six-month-old baby, having a negative ophthalmic and skin test, died immediately (three to five minutes) after the intravenous injection of 2 c c of antipneumococcus serum. There were no urticarial wheals, however, the death appeared to be associated with serum therapy. Unfortunately, an autopsy was not granted. The delayed reaction following serum therapy was seen rather frequently in varying degrees of severity. From thirty to sixty minutes after intravenous injection of serum a chill, occasionally slight cyanosis, dyspinea, and a thermal reaction, usually amounting to a rise of 2° F, have been observed. This type of reaction is constantly becoming less frequent with the increased refinement of serum. No such reactions occurred following intramuscular injection of serum.

## RESULTS

The distribution of the cases studied according to age group is given in Table I Only 2 of the 36 patients with bronchopneumonia reported were over two years of age

The group of infants treated with serum is smaller than the children's group because infants commonly have pneumonia due to pneumococci for which we have no therapeutic serum. Table II illustrates that 47 per cent of the 116 infants had lobar pneumonia due to an organism for which we have no specific serum, as compared to 32 per cent of the 278 children with lobar pneumonia.

The predominant infecting organism in the lobal pneumonia of children is pneumococcus. Type I, occurring in 325 per cent of all children's lobar pneumonia and in 47 per cent of the total 109 children in the treatable group. For infants, the predominant pneumococcus in the treatable cases of lobar pneumonia is Type XIV, representing 27 per cent of all infants' pneumonia and 336 per cent of the 116 treatable group. In infants with bionchopneumonia, pneumococcus. Type XIX occurred rather commonly and had a high mortality rate. This organism was frequently associated with streptococcus or hemolytic staphylococcus (5 of the total 11 patients, all of the 5 died). The significance of pneumococcus. Type XIX as the etiologic agent of the disease in such instances was difficult to determine. Three postmortem lung puncture cultures in these 5 patients had no pneumococci. The pre-

TABLE I
DISTRIBUTION OF TYPES OF PREUMOCOCCI IN SERUM AND CONTROL GROUP OF CASES

	1	1	TREA	ATED		1	UNTR	EATED		
TYPE	AOX		BAB		VCHO-		BAR	BEC	NOHO-	
4114	TEARS	PHET	MINOMIA	PNE	MONIA	PNEU	MONIA	PNE	AIGNIA	TOTAL
			DEATHS	TOTAL	DEATHS	TOTAL	DEATHS	TOTAL	DEATHS	
I	2 12	22				30	1			52
	under 2	_~	_~	i		8*	_ 2		1	3
П	2 12	4				4				8
	under 2				l				1.	G
IV	2-12	1	-			2	-			- 8
	under 2		_~_		L					. 0
v	2 12	3	~			8	-			6
	under 2		-			2		<u></u>		2
VI	2 13	5	~.	l <del>-</del>	-	10	٠.	1	1	10
	under 2		11	1	1	gt	8‡	8	8	_15
VII	2 12	1	-	-	-	3	-			4
-\iv	under 2		15	<del></del>		3			L	7
X14	2 12 under 2	17	2	1 3	2	1.	9	5	3	21 47
	2 12									
Δ,	under 2	] }		1		1 1		_		0 1
WIII	2 12							<del>-</del> -		0
.,	under 2			2	2			1	1	8
XIX	2 12			- <del>-</del>	<del></del>	i		<del></del> -		-0
	under 2		1	2	1	ĺĺ		Ð	8	11
XXII	2 12					-				0
	under 2			2	-	i		_	- 1	2
Mixed	under 2					1				1
types										
VI III,	'		i							
VI									LI	
XVII	under 2					1		1	-	1
	under 2							1		
vi, xviii	unuer 2							1	- [	1
VI, VII	under 2					<del> </del>		1	1	
XIV	under 2							1		<del>-</del> 1
Пі	under 2	:							_	-
XIX,	under 2	}	I					<u>1</u>		1
XI	unaci D	1	1		1			1	.	-

Excluded from study because no infants were treated with Type I serum. †Excluded from mortality table because case of meningitis complicating pneumonia

when treated,

‡Excluded from mortality table as meningitis complicating pneumonia when treated

two such cases.
 fExcluded from mortality group died of Staphylococcus aureus lung abscesses and empyema—autopsy

TABLE II
INCIDENCE OF LODAR PNEUMONIA IN INFANTS AND CHILDREN
(Bellevue Hospital January 1932—July 1933)

		NO. OF CA	SES	
AGE .	UNT	REATED		
(TEARS)	NO BERUM AV VILABLE	(CONTROL GROUP)	TRRATED	TOTAL
under 2	54	86*	261	116
2 12	51	65	44	160
Total	105	101	70	276

Including one case of meningitis.

fincluding two cases of meningitis and three Type I pneumoroccus in infants.

dominance of Type XIX might also be due to seasonal variation, there were more pneumococcus Type XIX infections both in patients with upper respiratory infection and with pneumonia in 1932-1933 than in the winter of 1932 Pneumococcus Type VI occurred frequently in infants in both lobar pneumonia and bronchopneumonia

The mortality rate for both bionchopneumonia and lobai pneumonia is shown in Table III

TABLE III
MORTALITY RATE IN TREATED AND CONTROL GROUP

	BEO/CHO		I OBAR PNEUMONIA		LOBAR PNEUMONIA AND BRONCHO PNFUMONIA		MORTALITY PER OENT
	TOTIL	DEATHS	TOTAL	DEATHS	TOTAL	DEATHS	
Cases treated	12	6	69*	2	81	8	98
Cases untreated	24	17	96†	3	120	20	166

<sup>\*</sup>Excluding one case of pneumococcus maningitis complicating pneumonia when treated

Although the percentage of mortality for the treated cases is lower than that for the control group, the entire series is too small to warrant a definite conclusion as to the efficacy of serum in reducing the mortality rate

The bronchopneumonia group is small, not because of the infrequency of the disease, but because we are more often unable to obtain pneumococci from repeated larvingeal swabs. Of the 90 patients with bronchopneumonia studied, only 50 had pneumococci in the cultures from larvingeal swabs. Of these 50, 26 died and cultures of postmortem lung punctures made immediately after death on 7 showed hemolytic staphylococci or streptococci, but no pneumococci could be isolated, from 9 patients pneumococci were cultured from postmortem lung punctures. No postmortem lung puncture was done on 9 of the 26 patients, and 1 puncture was sterile

An objective criterion for the efficacy of antipneumococcus serum in lobar pneumonia is shortening the duration of the disease. A crisis usually occurred from twelve to twenty-four hours following the introduction of serum therapy, frequently after the administration of only 7 to 10 cc in twelve hours' time. In infants, this period is prolonged from twenty-four to forty-eight hours. The crisis was judged by fall in pulse rate and respiratory rate, and other evidences of loss of toxicity.

Charts 1 2 and 3 show the effect of serum on the duration of the disease. The day of crisis of all patients with lobar pneumonia due to pneumococci for which we have the apeutic serum is given in Chart 1. A crisis was observed by the fifth day of the disease in 60 per cent of the

fExcluding two cases of pneumococcus meningitis associated with pneumonia and three infants with Type I lobur pneumonia

49 patients treated with scrum as compared to 20 per cent of the 79 patients in the control group. Many of the scrum treated patients had a crisis before the fifth day of the disease.

The most consistently satisfactory results have been obtained with pneumococcus Types I and XIV serums Chart 2 illustrates the day

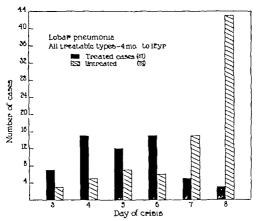


Chart 1—Duration of disease in all patients receiving serum compared with a control untreated group. Greater number of treated cases show early crisis.

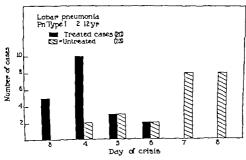


Chart 1.—Duration of Type I pneumococcus pneumonia among treated children compared with untreated control group. The course of the disease is definitely short r in the treated group. Seventy fire per cent of the treated patients had a crisis before the 11th day as compared with 10 per cent for the centrol group.

of crisis of patients with pneumococcus Type I pneumonia in children. It can be seen at a glance that serum definitely shortens the disease, a crisis as early as the third day in 5 of the 20 treated cases is noted,

whereas not a single patient of the 25 untreated cases had such an The duration of the disease was never longer than six days early crisis in any patient receiving serum (Type I), while in 16 of the 23 control group a cusis occurred after the sixth day. In short, 75 per cent of the treated patients had a crisis before the fifth day as compared to 10 per cent for the control group Antipneumococcus Type XIV serum has been similarly effective in shortening the disease in both infants and children as shown in Chart 3 The duration of lobar pneumonia in infants on the average is several days longer than in children the 18 patients receiving serum had a crisis later than the seventh day, while the duration of the disease in 18 of the 27 untreated patients was longer than seven days In other words, a crisis was observed in 80 per cent of the 18 patients before the seventh day as contrasted with 19 per cent (5 of the 27) of the control group

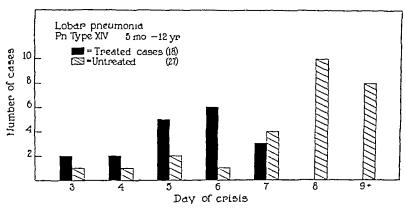


Chart 3—Duration of Type VIV pneumococcus pneumonia of control and treated group for all ages. The treated patients had later crises eighth and ninth days no similar case in the treated group. The disease is shorter in the treated patients.

Although Chart 1 definitely suggests that serum is efficacious in shortening the disease, all serums are not equally effective. Chart 1 represents largely (80 per cent treated, and 63 per cent untreated) the results with antipneumococcus serums Types I and XIV. On the other hand, the results of antipneumococcus Type VI serum do not seem to have been so decisive. An analysis of 21 patients, 7 treated and 14 un treated, reveals no appreciable difference in the two groups. In fact, 2 until ited patients had a crisis as early as the third day, whereas the cribicst for the treated group was the fourth day. A probable explanation for these observations aside from the possible inefficacy of antipneumococcus Type VI serum is the difficulty of diagnosis. Since pneumococcus Type VI A and B is a frequent inhabitant of the throats of infants and children, errors in diagnosis with this organism may be easily made.

The medical histories were taken with great care to determine the exact day of onset of the pneumonia, nevertheless, there was a small

number in each group in which the duration of the disease was inde terminate due to inability to dute the enset or to date the crisis, as for example, in the development of an empyema

On the whole, the scrum treated group showed signs of greater tox ieity before treatment than the nontreated group. This observation is in part indicated by the fact that there was a greater number of two lobe pneumonias in the scrum group, 13 of the 69 (18 per cent) treated patients had two or more lobes involved, whereas only 8 of the 94 (8 per cent) control group had pneumonic consolidation of more than one lobe

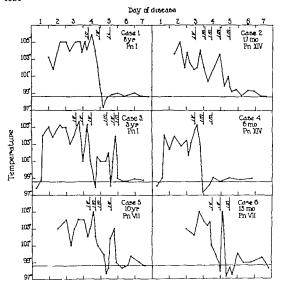


Chart 4.—Temperature curves of selected patients, showing usual response to antipreumococcus serum in lobor preumonia. The arrow represents serum administration
of Types I. XIV and VII antipueumococcus serum, intravenously (Lv) or intra
muscularly (lun). Cases 1 and 4 indicate a common type of response. The interdevaloped lobar pneumonia in the hospital Case 3 also developed lobar pneumonis
in the hospital and illustrates the result of inadequate treatment a second dose
of serum should have been given on the fourth day of the disease. Small quantities
of serum were used in Cases 1 4 5 and 5.

The response to the administration of serum can best be seen by reference to the temperature charts of a few selected cases showing typical response (Chart 4) Pneumococcus Type I is the predominant type for children and Type XIV for infants in this series. The thermal reaction following intravenous injection is also shown, particularly in Case 3 where a certain lot of serum having a high content of chill producing

fraction was used. The loss of toxicity following serum administration is as impressive as the drop in temperature and is correlated with it, sometimes antedating the final temperature fall to normal. Case 2 illustrates the use of intramuscular serum injections after an initial intravenous dose.

Patients with bronchopneumonia show a different response to serum treatment. A crisis is not usually observed as in the lobar pneumonia group, and hence a fall in temperature cannot usually be used as a criterion for the efficacy of serum. We treat bronchopneumonia patients for only forty-eight hours, using the dosage of from 500-1000 units per pound of body weight for a twenty-four-hour period (or 10 15 ec. in 3-4 doses per day). Chart 5 represents the temperature curves

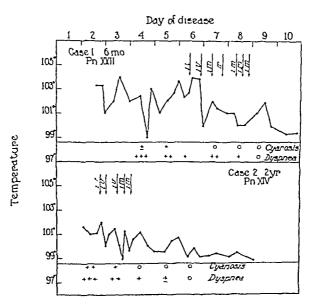


Chart 5—The temperature curve of two patients with bronchopneumonia receiving antipneumococcus serum Types XXII and XIV Temperature response is not like that in lobar pneumonia. (See Chart 4) Improvement is clinical as indicated below in decreasing cyanosis and dispinea. More frequent and larger dosages of serum are necessary in bronchopneumonia

of patients with bronchopneumonia who received serum. Both patients were very sick, with evanosis and marked dyspinea. These symptoms were practically lost after forty-eight hours of treatment and were diminished after only twenty-four hours. There is no crisis, however, and a comparison of these temperature curves with those in Chart 4 riveals this fact.

A study of the duration of the disease with reference to the period of hospitalization is shown in Chart 6. It becomes apparent that admission to the hospital carly in the disease does not in itself act to shorten appreciably the duration of Type I pneumococcus pneumonia in the same age group. To illustrate, 13 patients admitted to the hospital

on the second day of the disease received serum. All of these patients had a crisis by the end of the fifth day and most of them before. The 9 patients who had equal hospital care but no serum admitted on the second day of the disease, continued to run a long course with the crisis on the sixth to ninth day. Although the serum treated group has a greater number of patients with early hospital admissions, Chart 7 clearly indicates that this factor in itself does not tend to shorten the disease.

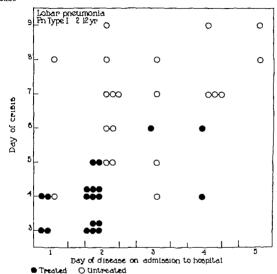


Chart 6—Duration of the disease in treated and control groups with reference to period of hospitalization in pnounecocous Type I pnounonia Each untroated patient is represented by an open circle socia treated patient, by a black circle. Although more serum treated patients were admitted to the hospital early in the disease this factor alone does not shorten the disease. Patients untreated admitted on the same day of illness have a longer course.

Finally, only one patient of the 69 cases of lobar pneumonia treated with serum developed empyema. This seven year-old child had 2 doses of pneumococcus Type V serum a total of 10 c.c. 15,000 units on the fifth day of the disease and a crisis ensued. The empyema Type V was demonstrated after an afebrile period of three weeks. Of the 94 cases in the control group 4 developed empyema, two of the pneumococcus Type I origin, one pneumococcus Type XIV, and one Type V. A spread of the pneumonia to a new lobe was observed in 2 patients in the control group. There was no such complication in the treated group. No

patient receiving serum developed meningitis. Preumococcus meningitis Type XIV was diagnosed in one patient in the control group, 3 infants had preumococcus meningitis Type VI, all of whom died. One of these 3 infants received intravenous and intrathecal antipreumococcus serum. All 3 of these infants are evaluded from the mortality rate.

The above facts tend to indicate that the complications following lobar pneumonia may be decreased by administration of antipneumococcus serum. Perhaps this difference is in part due to the fact that all the

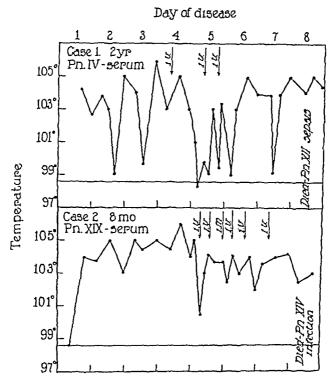


Chart 7—Temperature curves of two patients falling to respond to serum. Case I is that of a two year-old boy having Types IV and VII pneumococci in the laryngeal swabs. Serum for Type IV was given (no therapeutic serum for Type XII). Blood culture taken before treatment was positive for pneumococcus Type XII. Patient dled with pneumococcus type XII sepsis and maningitis. Case 2 was treated with antipneumococcus Type XIV, the type obtained from 2 laryngeal swab cultures. No response to treatment. Pneumococcus Type XIV empyema developed. Probably an error in diagnosis of the etiologic agent was made. Pneumococcus Type VIX is most likely a nonpathogenic inhabitant of the throat.

serum treated group received serum relatively early in the course of their disease. It seems significant that the one ease that developed emprema following serum therapy, received treatment late in the disease.

That pneumococci may be found in the throat of a normal person is a well known fact. It becomes difficult at times to evaluate the presence of pneumococci in cultures from larvingeal swabs, as is illustrated in Case 2, Chart 7 Pneumococcus Type XIX was cultured from two larvingeal swabs and from the pus from the ear of a baby with lobar

pneumonia (confirmed at autops) Antipnoumococcus serum Type XIX produced no appreciable improvement in the patient's condition A pneumococcus Type XIV empyema, septicemia, and meningitis en sued, with subsequent death. In this patient, it seems reasonable to assert that the death was not due to failure of antipneumococcus serum but rather to a failure in the diagnosis of the etiologic agent.

Multiple pneumococcus infections are confusing also, but fortunately were infrequently found in the group reported. It was more commonly found in the group for which we have no serum. Case 1 (Chart 7) is that of a child having both Types IV and MII pneumococci in equal proportion in the culture from the largingeal swab. A blood culture was taken before the administration of antipneumococcus serum Type IV. Therapeutic serum for Type XII was not available. The following day a report of the blood culture revealed only pneumococcus Type XII, a fatal meningitis developed and pneumococcus Type XII was cultured from the spinal fluid. Repeated largingeal swabs revealed only Type XII pneumococcus.

Cultures of lung suction punctures might help in determining the true etiologic agent of the disease in such cases as the 2 cited above and also in patients with bronchopicumonia where the pneumococci, even when found frequently may not be the true or sole etiologic agents Pneumococci isolated from patients with bronchopneu monia are often associated with hemolytic streptococci or hemolytic staphylococci On postmortem lung puncture cultures of patients with such mixed bacteriology hemolytic staphylococci or hemolytic strepto cocci are usually found without pneumococci. Autopsy in many of these patients disclosed multiple abscesses in the lungs. Hence, it is suggested that even though pneumococci are found in the cultures from the larvingeal swabs of babies with bronchopneumonia these organisms in many instances are probably not the etiologic agents of the disease Blood cultures and cultures of other body fluids on a number of babies have been positive for streptococci even though pneumococci have been cultured from the swahs

Although the largngeal swab method of culture does lead to errors as indicated, on the whole it is a more feasible method than lung suction puncture and is satisfactory for the lobar pneumonia group in a very high percentage of cases.

Perhaps the more striking results of antipneumococcus Type I serum therapy is partly attributable to a greater accuracy in diagnosis of the type of infecting organism in patients with pneumococcus Type I pneumonia. During this investigation a moderate number of children and infants with acute pharvingitis and acute bronchitis were studied bac terrologically. Preumococcus Type I was found only once in these cultures, whereas other types of pneumococcus were isolated rather com

# HISTORY OF PREVIOUS PREGNANCIES

Twenty-nine of the mothers compusing this group were primiparas. Thirty-eight mothers gave a history of having had a total of 68 abortions. Eleven mothers had a total of 18 stillborn infants, and 12 others had previously borne 19 live premature infants. Six of these mothers had both abortions and stillbirths, or both abortions and previous prematures. Twenty-three mothers had had full-term in fants, with the premature infants noted here as their first early termination of pregnancy.

## TREATMENT OF MOTHERS

In general the parents dealt with have been careless about then own treatment. Only 13 of the 97 mothers are known to have received antenatal treatment and none of these received a sufficient amount as measured by present standards. Most mothers who went to prenatal clinics, visited them late in pregnancy or immediately before delivery. Three of the infants born of this group of treated mothers died shortly after birth. In one of these infants, evidence of syphilis was found at autopsy

TABLE III SIMPTOMS\*

Snuffles	26
Enlarged hver	11
Enlarged spleen	$\hat{\tau}$
Desquamation	16
Indurated shiny palms and soles	10
Fissures	9
Rash	7
Mucous patches	1
Hemorrhage	9
Edema	4
General appearance	3
Adenopathy	2
Failure to grin	4

<sup>\*</sup>The limited number of some of the manifestations recorded is in large part due to the fact that treatment was started immediately upon the report of politic serologic findings in one or both parents even though the infants showed no signs of disease

## SI VIPTOVIS

Forty-eight infants did not have recognizable clinical signs of syphi-The symptoms noted in the remaining 70 are listed lis at any time Snuffles was the most frequently noted symptom, occurın Table III ring in 26 infants In 6 of these the discharge was bloody these infants had a saddle nose deformity at birth The usual time of appearance of snufiles was between the third and the fourteenth day Characteristic desquamation involving the palms and soles, and the face usually associated with other signs of syphilis, occurred in 15 in An enlarged liver was found in 11 babies 7 of whom also had Bleeding fissures about the nose mouth or anus an enlarged spleen occurred in 9 infants Edema was present in 4 infants involving particularly the lower limbs, abdomen, and scalp. An eruption was recorded in 10 cases, in 9 of which it was maculopapular in type, in the other one mucous patches occurred. Hemorrhage was present in 9 of these infants accompanying unmistakable clinical signs of syphilis. The bleeding came from the rectum in 6 infants, the stomach in one, the vagina in one, and generalized eechymosis occurred in one other.

#### RELATIONSHIP OF SYMPTOMS TO EARLY MORTALITY

Thirty two of the premature infants died during their stay in the hospital, as listed in Tables I and II. Nine of these died within twenty four hours after admission, which was usually a few hours after their birth. Tourteen more died within two weeks, and the remaining 9 died before reaching the age of two months. Twenty-one infants had severe symptoms of syphilis shortly after birth, and of these, 18 died despite treatment. At postmortem, besides syphilitic changes observed, 2 had intracranial hemorrhage, 2 had bronchopneumonia, and 1 pneumococcic meningitis. Five infants who died weighed under one thousand grams of the 12 remaining infants, syphilitic changes were found in 5 at post mortem examination. Death was due in 5 instances to intracranial hemorrhage in 2 to atelectasis, and in 2 to bronchopneumonia.

### TREATMENT

Antisyphilitic treatment has been started in each infant routinely, upon the discovery of a positive Wassermann reaction in either parent We feel that immediate treatment is justified for several reasons First a premature interruption of gestation in a syphilitic mother even though she has been treated during pregnancy is presumptive evidence of syphilis in the infants Second, the earlier the treatment is instituted the better the prognosis, except in cases of severe visceral syphilis, and third as Wile and Shaw 13 von Mettenheim 21 and others have observed it is becoming increasingly difficult to make a diagnosis These observers note that the picture of congenital syphilis early of congenital syphilis has changed due to the treatment of mothers during pregnancy, so that very few of the infants show definite clim cal evidence of the disease at birth. If these infants are allowed to go untreated, the disease may manifest itself as late as puberty, or even later

Some American observers who begin treatment before the manifestation of symptoms are Atlee and Tyson 22 who immediately treat all infants who have positive cord Wassermann reactions. McCord<sup>22</sup> also advocates this. Dunham<sup>24</sup> treats all offspring of mothers who have had an active or recent syphilitic infection and have not received

Bables born at hone or in haspituls other than Michael Reese who need incubator care, are usually transported by special ambulance to the Sarah Morris Premature Station immediately attre birth

treatment antenatally Wile and Shaw<sup>13</sup> believe that treatment should be instituted for all infants born of mothers with recent syphilis, even though treated during pregnancy. Kolmer-o noted that it was advisable to regard every child of syphilitic parentage as infected, and administer antisyphilitie therapy even though the infant appears healthy and gives a negative Wassermann reaction, especially if either parent is uncured. Taylor believes that all children born of syphilitic mothers treated during pregnancy, should be treated prophylactically for at least two years.

There are many European observers who believe that treatment should be given at birth to all offspring of syphilitic paients, regardless of the duration of the infection, and also to supplement the prenatal treatment given to the mother Klaften2" believes that every descendant from syphilitic parents should be subjected to prophylactic treatment. He noted that the mortality of infants with congenital syphilis was around 30 per cent, and that the mortality of those treated immediately was only 91 per cent. In view of this fact, he undertook preventive treatment in apparently healthy children born of syphilitic parents with a result that the mortality was reduced to 79 per cent. In another article, the same author28 states that such authorities as Galliot, Jadassohn, Fischl, Finkelstein Davidsohn, Pazzke, Pinard, Slavik Noeggiath, Richter Eisch Muller, and others advocate the preventive treatment in newborn infants of syphilitie Hoffman<sup>20</sup> believes that infants born of syphilitic mothers who have had a more or less energetic treatment during pregnancy, should be subjected to preventive therapy. He states that one must take exception to the rule, "no treatment without previous diagnosis"

Adams, in discussing a paper by Nabarro<sup>30</sup> stated that the battle in congenital syphilis is over in the first two or three months, and so institutes immediate treatment in all infants, even if their mothers had prenatal therapy Marfan<sup>31</sup> suspects the presence of congenital syphilis in infants born of infected parents, even when no certain signs of the disease exist, and even when the Wassermann reaction is negative, he would treat the infant as if the disease were certain Pillsbury32 believes that it is haidly logical to regard the almost cortainly infected infant of a mother with early syphilis as cured by prenatal treatment. He notes that at the Welander homes, in the Scandinavian countries, where the long-continued observation of syphilitie mothers and children is unparalleled, it is the custom to continue treatment of the infant after birth regardless of the absence of syphilitie symptoms Scherber,33 von den Steinen,34 and Lereboullet,20 also believe that all offspring of syphilitic parents should be subjected to prophylactic treatment

While these observers are in the majority, there are many authorities who take an opposite stand. Boas<sup>30</sup> is strongly opposed to treat-

ing any child until the diagnosis is definitely established. Buschke and Gumpert<sup>17</sup> conclude that a child of syphilitic parents must by no means necessarily be infected, and they are very careful in the selection of children for prophylactic therapy. Hahn<sup>28</sup> institutes treatment in the offspring of syphilitic parents when their Wassermann reaction is negative only if they fail to gain properly in weight.

### METHOD OF TREATMENT

Until the past twelve months, the routine treatment, either prophy lactic or in the presence of symptoms, was to use mercury in the form of inunctions combined with oral administration of mercury and chalk, together with sulpharsphenamine injected intramuscularly. Mercury with chalk was started in the small dosage of one eighth grain daily because of the ease with which it causes diarrhea in very small in fants. The dose was increased until infants one year old were receiving one grain three times daily. Inunctions of five grains of mercury ointment were used only during their stay in the hospital, and were given once daily for seven days, with seven days' rest. Sulphars phenamine, in a dosage of 0.002 grain per kilogram of body weight, was injected once a week for six weeks with six weeks of rest and this course was repeated twice during the first year. The mercury with chalk was given during the same time that the arsenical was being administered.

### STOVARSOL THERAPY

During the past year, stovarsol has been the only drug employed in our clinic. Stovarsol acetarsone, or acetylaminohydroxyphenylar some acid, known as 'spirocid'' in Germany, contains 27 1 to 27 4 per cent arsenic and is a white powder odorless, with a slightly acid taste It is manufactured in the form of 0.1 gram and 0.25 gram tablets. The 0.1 gram tablets are the only ones which were used in this study. A complete description of this drug is given by Maxwell and Glaser.

The dosage given to infants as reported in the literature varies markedly in amount. Thus, Soldin and Lesser ogive doses to infants in increasing amounts as follows

14 0.25 gram tablet once daily for three days

14 0.25 gram tablet twice daily for three days 14 0.25 gram tablet 3 times daily for three days

14 0.25 gram tablet twice daily for three months and from them on

1/2 0.25 gram tablet 3 or 4 times daily until a minimum total dosnge of 35 grams had been administered

Tuscherer 41 working in the University clinic in Berlin, also used large doses both in infants and older children. His regimen was to give the following

以 0 25 gram tablet once daily for three days

14 0.25 gram tablet 2 times daily for three days

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14 0 25 gram tablet 3 times daily for three days
14 0 25 gram tablet 4 times daily for three days
15 0 25 gram tablet 4 times daily for three days
1 0 25 gram tablet 2 times daily for three days
1 0 25 gram tablet 3 times daily until a total dosage of 21 grams in forty one days was given. At least one more similar course was repeated, even though the infants had a negative Wassermann reaction at the end of treatment.
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Klaften gives newborn infants one-half of a 0.25 giam tablet the first day after birth. During the first week he gives three and one-half tablets combined with mercury. The whole course of prophylactic treatment thus instituted lasts eleven or twelve weeks, during which time fifteen grams, or sixty 0.25 gram tablets are administered. In premature infants, however, he gives smaller quantities. One-quarter of a 0.25 gram tablet is given the first day of the first week of treatment, and half a tablet the remaining six days. In the second week, one half tablet twice daily is given, and without further increase a total of four to six grams is administered.

Smaller doses are advocated by some Oppenheim and Fessler<sup>42</sup> give a daily dose of 0.01 to 0.03 gram to newborn infants, and to nurshings up to six months 0.05 to 0.12 gram daily Courtin,<sup>43</sup> quoting Danzer, reports that his system is to give a daily dose of 0.01 gram for three months, giving a total dose of only four to five grams of the drug Kiosl<sup>44</sup> recommends a dose of 0.02 gram per kilogram of body weight for four consecutive days each week for six of eight weeks Other observers, Erich Muller,<sup>45</sup> von den Steinen,<sup>34</sup> Wegner,<sup>46</sup> and Bleschmann<sup>47</sup> also believe that a rest should be given after several days of treatment to allow the patient to eliminate the arsenic taken

Scherber<sup>33</sup> gives three 0.1 gram tablets daily and increases the dosage to six tablets daily. He obtains the permissible total dosage by dividing the weight of the child in kilogiams by four. Thus, a ten-kilogram infant would receive 2.5 grams in a total course.

Bratusch-Marram<sup>48</sup> recommends that the drug be given in relation to the body weight of the infant. He gives the following

```
0 005 gram per kilogram daily for 1st week
0 010 gram per kilogram daily for 2nd week
0 015 gram per kilogram daily for 3rd week
0 02 gram per kilogram daily for 4th week
and continues at this dosage for five more weeks,
after which a rest period of six weeks is in
stituted
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Since extreme care in administering arsenic to young infants is always necessary it appears that this type of dose is advisable. I have used this system advised by Bratusch-Marrain, 48 after seeing it used

so successfully by Abt and Traisman\*4 at Northwestern University Clinic. This method has also yielded excellent results when used by Rosenhaum \*0

Three such courses are given the first year, and are continued at least one more year Wassermann tests are made at the end of each rest period.

Thirty two infants have been treated with stovarsol. Of these, 8 have had this drug alone 7 have had mercury in combination with stovarsol, and the remaining 17 have had previous courses of mercury and sulpharsphenamine.

EFFECT OF STOVARSOL ON SYMPTOMS AND ON WASSERMANN REACTIONS

In 9 infants who had snuffles the condition cleared up in from four to eight weeks. Five of these infants received mercury and chalk to gether with stovarsol, with no more rapid change in symptoms than those on stovarsol alone. Five infants had splenic and hepatic en largement. In 3 of these the liver and spleen were no longer palpable at the end of one course of therapy, in the other 2 the liver was no longer palpable at the end of two courses, but the spleen was still enlarged. It was however, in each case, smaller than when originally noted, and much less firm in consistency.

Six of the 17 infants who received stovarsol after having previously been treated with mercury and sulpharsphenamine, were under one year of age. All of these infants were clinically and serologically negative when stovarsol treatment was begun. Stovarsol was used simply to complete an adequate amount of therapy

The blood Wassermann and Kalm reactions have been negative after one course of therapy in all the infants treated with stovarsol, or with mercury and stovarsol, and all have remained so. Twelve infants have had 3 negative reactions when taken at the end of each rest period, and 3 have had two such negative reactions. One infant who had a two plus Wassermann and Kahn reaction following the use of one course of mercury and sulpharsphenamine, had a reversal of the reaction following the added use of one course of stovarsol. The reaction remained negative on two further examinations

A favorable effect of stovarsol on the Wassermann reaction in in fants with syphilis has been reported by all authors. Abt and Trais man had positive Wassermann reactions reversed after treatment in 14 out of 18 infants. Rosenbaum reactions in all of 9 children who had treatment begun during their first year. Maxwell and Glaser treated 10 infants under one year 4 of whom had negative Wassermann reactions at the start that remained negative while 6 others with positive Wassermann reactions.

Infants are brought to the clinic each week and only enough of the drug to last one week is given. It is advised that the drug be dissolved in water or weak tea and given thirty minutes before a feeding.

14 0 25 gram tablet 3 times daily for three days
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 15 0 25 gram tablet 4 times daily for three days
 1 0 25 gram tablet 2 times daily for three days
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cellaneous and unknown, 161 cases Hustenss investigated the fate of 39 cases of congenital syphilis and found that one half died of inter current infections, with only 16 hving at the time of his study Antoniewicz reported that 15 of 46 children, or 32 4 per cent, treated after manufest symptoms occurred, died (10 before reaching the age of one year), while in a group of 36 infants born of syphilitic parents and treated prophylactically from birth on, only 6 per cent died, and all of these were over one year of age Lange's observed 100 syphilitic infants for ten years. Sixty seven of these died, 52 from respiratory and intestinal diseases. Ten of the infants were premature, and only one survived. He noted that even though symptoms of syphilis had disappeared after treatment, the children withstood infections poorly White and Vecders reported the results of treatment of 197 cases, less than two years of age Sixty died, or a mortality of 30 1 per cent. Fourteen of the infants treated were premature, and 6, or 43 per cent. of them died

Forty of the 58 infants followed in the clinic have had infections of varying degrees of severity. All of these infants have had one or more attacks of nasopharyngits and 15 have had out in media. Bron chopneumonia occurred in 10 infants, bronchitis in 4, cervical adentis in 3, pyelitis in 1 and gastroenteritis in 6

Premature infants are naturally more susceptible to secondary in fections because of their size and lack of immunity to disease so that the infections that occurred in this group cannot necessarily be blamed on a lowered defense mechanism due to syphilis. The hygienic sur roundings of this group of infants at home have been very inferior and it is probable that exposure to respiratory infections in particular has been frequent.

Mild symptoms of rickets occur with frequency in many premature infants even with adequate prophylactic therapy. Four of this group developed moderately severe rickets. Three of these infants were negroes

One infant in this group had hydrocephalus, and one had spina bifida occulta. Otherwise, no abnormalities have been discovered

At the present time there are under observation in the premature clinic 38 of these children. Twelve of them are over two years of age, 11 are between one and two years and 15 are under one year. Fifteen others were treated for at least two years, but have since been lost track of. Two others over two years of age are now in institutions. During the time that the infants were under clinic care, only 2, or 3 44 per cent, died. One of these the infant before mentioned as having a strongly positive Wassermann reaction after treatment, died at the age of sixteen months from arsenic poisoning following an injection of sulpharsphenamine in the third series of treatment. The twin sister of this child died a short time afterward at home from what was probably bronchopneumonia.

		TABLE IV	
INFLUENCE	оF	TREATMENT ON	WFIGHT

	NUMBER OF INFANTS	AVERAGE WEIGHT AT SIX MONTHS	AVERAGE WEIGHT AT TWELVE WONTHS
Normal	200	4025	6100
Sulpharsphenamme	43	3760	6035
Stovarsol	8	3780	6647

Improvement in general body tone and weight is always noted in syphilitic infants while under treatment. In Table IV the average gains made during six months and one year are noted. The average listed under the heading "normal" was obtained from all of the non-syphilitic infants brought to the clinic during the past two years. Gains during the first six months are very much alike in each group, while the average gain for the whole year made by the infants who received stovarsol is over 500 grams greater than the gain for the nonsyphilitic group for the same length of time. It must be remembered that this group treated with stovarsol is much smaller in number than either of the other groups. Improvement was often noted as soon as stovarsol was started, while these same infants did not do particularly well during the six-week rest periods. Increase in appetite and activity was frequently reported by the mothers.

Tezner,50 noting the marked improvement in treated syphilitic infants, advocated the use of stovarsol in dystrophic and poorly thriving nurslings Lesser and Soldin<sup>40</sup> especially emphasized the gain in weight of syphilitic infants treated with stovarsol and traced this to the favorable effect of the arsenic Von Mettenheim<sup>21</sup> states that be sides the specific effect of stovarsol on syphilitic lesions, the drug has a tonic effect. He found in the 18 infants which he treated, that the weight and general health improved, and the hemoglobin rose rapidly Niederwieser o used stovarsol in nonsyphilitic infants suffering from anorexia and loss of weight and reported good results Marram48 emphasized the good effects of spirocid treatment upon the physical development of those infants so treated Juarros and Galarreta," in treating 40 older children with spirocid, reported that the most constant effect of the drug was an increase, sometimes very accentuated, in weight and height Tuscherer observed that children with congenital syphilis, except those with severe visceral lesions, improve physically during the course of treatment with stovarsol, which He found that the weight curves rehe attributes to the arsenic sembled those of healthy infants

# TOXIC SIMPTOMS RESULTING FROM STOVARSOL

All observers note that toxic effects from arsenic are less marked in infants than in older children. Soldin and Lesser<sup>10</sup> reported mild

Herxheimer reactions in infants as did Krombach 32 After the drug was discontinued for some time, it was well tolerated again

Toxic symptoms resulting from stovarsol or spirocid occur fre quently, but they are usually mild. In infants the most frequent toxic manifestations are diarrhea, vomiting, cutaneous symptoms, and fever Diarrhea has been noted by many observers. Krombach<sup>22</sup> reported occasional attacks in infants that she treated. Guillemot<sup>22</sup> noted that slight digestive disturbances occurred frequently. Huber<sup>23</sup> reported that 3 infants out of 16 treated developed diarrhea. Bratusch Marrain stated that some infants receiving his customary dosage showed frequent and thin stools, but these never took on an alarming character, and always disappeared rapidly after the drug was discontinued Abt and Traisman, 4 and Maxwell and Glaser<sup>40</sup> have noted mild diar rheas in some of the infants they treated

Exanthems of a morbilliform and scarletiniform type have been frequently noted as have urticarial and bullous lesions

Transient albuminuria has been found by Abt and Traisman, and Maxwell and Glaser . The latter authors treated 2 infants who developed a generalized flaccidity, one of whom died

In the 32 premature infants that I have treated with stovarsol there have been three who developed a mild diarrhea. In each case this has occurred during the fifth or sixth week of therapy after a total dosage of from 25 to 3 grams of the drug. The looseness of the stools ceased shortly after the withdrawal of the medication, and treatment was started again after a lapse of one week, with no further upset

Two infants developed an urticarial rash on the extremities which disappeared within one week after temporarily discontinuing the drug

One infant twenty four days old, developed a diffuse redness of the skin over the face, trunk, and extremities, which was followed by a generalized desquamation. No constitutional symptoms accompanied this and the infant gained four hundred grams in the two weeks that the desquamation continued.

In most cases it has been difficult for the mothers to obtain regular specimens of urine from the infants treated. A trace of albumin was noted transiently in 11 of 20 infants and children whose urine was examined. No abnormal microscopic findings have accompanied this albumin, and it has not been considered a contraindication to the continued use of the drug

### COMMENT

The earlier antisyphilitic treatment is started in congenital syphilis, the better the chances for a normal infant and a serologic cure. Many infants who have congenital syphilis do not show signs early, and often the early signs are so mild that it is difficult to interpret them. An extensive review of the literature reveals that it is considered

wise, particularly abroad, to subject all offspring of syphilitic parents to prophylactic therapy, especially where there has been a recent infection, and where mothers did not have sufficient antenatal treatment It is difficult and probably wrong to label a child from such a parent as syphilitic without clinical or laboratory evidence of the disease, but if one is to wait for this evidence, much valuable time may be lost, resulting in the failure to secure as good results as might have been obtained through early treatment. Where treatment involves the use of intramuscular injections, it is impossible not to brand the child as syphilitic, while if a peroral form of treatment can be used, it is simple to advise and employ this form of therapy without stigmatizing It is extremely difficult to have patients return regularly for injection therapy, while no lack of cooperation has been evidenced with the simple dispensing of the stovarsol tablets. When the parents can actually see an improvement in the infant as far as gains in weight and body turgor are concerned, occurring during such periods of therapy, they are usually anxious to come to clinic regularly for the medication

While in all probability many of this group of infants did not have syphilis, the mortality of only 3 44 per cent is evidence that the prophylactic treatment has been of great value. The Wassermann reaction in all infants and children so treated has been negative, and no later signs of syphilis have as yet occurred.

## SUMMARY

- 1 At least two years of treatment, either prophylactic or curative, is advised for all premature offspring of syphilitic parents
- 2 Fifty-eight infants have been treated prophylactically or curatively for congenital syphilis. Of these 8 have received stovarsol alone, 7 have had mercury and chalk in conjunction with stovarsol, and 43 have had mercury and sulpharsphenamine. Of the latter group, 17 have had stovarsol in their second year of treatment.
- 3 While no attempt is made to compare the results obtained by either form of therapy, stovarsol by mouth is advised because of its ease of administration, and the resulting cooperation of the parents
  - 4 No serious toxic symptoms have resulted from the use of stovarsol
- 5 Early treatment has resulted in a known mortality of only 344 per cent of the infants discharged from the premature station to their homes, 279 per cent of the total 118 having died during their original admission to the hospital

The stovared used in this study was furnished through the courtesy of Merck & Co

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# GROWTH PROBLEMS

II BASAL METABOLIC RATE VARIATIONS IN RELATION TO BODY BUILD
ADOLESCENCE AND ALLERGY IN CHILDREN

WILLIAM PALMER LUCAS, M D , HILLEN BRENTON PRYOR, M D , CRAWFORD BOST, M D , AND SANTON T POPE, JR , M D SAN FRANCISCO, CALIF

A STUDY of 1,334 basal rate determinations on 680 normal children shows every gradation from high to low rate. The rates plotted follow a typical normal distribution curve similar to the distribution curves of any other biologic data in a large series.

Symmetrical variation above and below the average is seen in the normal distribution curve of any trait, the majority of cases being classified normal, whether the data are height or oxygen consumption or introversion. It is necessary to plot the entire curve of distribution in order to recognize degrees of deviation, and the total curve should be kept in mind in diagnosing normal functions for any individual

## BODY BUILD FACTOR IN BASAL METABOLISM

Parallel studies of basal metabolic rate and body build in 415 children showed a definite relationship between thyroid activity and type of body build. High basal rates were the rule for the slender-built and low basal rates for the broad-built. Oxygen consumption was compared with body build by means of the Pearson correlation coefficients. The relationship between percentage deviations from average calories per kilogram body weight per hour, and from average width length index of build for age and sex were as follows.

177 boxs Ages 3-17 years  $r^* = -0.196 \pm 0.049$ 238 girls Ages 3-17 years  $r = -0.262 \pm 0.041$ 

These negative correlations showed that degrees of slenderness below average of body build were related to degrees of increase above average in oxygen absorption in this group of 415 children. In other words the difference in relative width of the body (measured by the width-length index) seemed to be a determining factor in oxygen absorption when both were on a unit basis.

Our approach in the present study, being medical and not surgical, has employed the basal metabolic rate as its method for recognizing levels of glandular function. Consequently, the classification of the children has been in terms of basal metabolic rate variations. Recognizable pathologic thyroid abnormalities have been eveluded from this study.

<sup>\*</sup>r equals the Pearson coefficient of correlation

If biopsy were feasible we wonder if even these remaining thyroids might not show histologic staining differences consistent with varying degrees of secretory activity. We have considered this series to represent hypo- and hyperfunction without hypo and hyperplasia. We have not seen any progressive tendency toward the pathologic entities

What determines the levels of glandular activity is debatable, all though suspicion falls strongly on inheritance. Physical type, how ever, seems to be almost invariably a consequence of glandular state.

The groups called linear and lateral undoubtedly are to be associated with thyroid hyper and hypofunctions respectively and the body changes induced by extreme gross pathologic thyroid states are unquestioned and diagnostic

Our basal rates were referred to the Benedict Talbot standard They were done after one half hour rest in the postabsorptive state, and represent at least two consecutive determinations that cheek.

#### HIGH BASAL METABOLIC RATES IN SLENDER CHILDREN

One hundred and ten of our 680 children had basal metabolic rates of 20 per cent plus and over but exhibited none of the cardinal toxic

TABLE I
HIGH BABAL METABOLIC RATES IN SLENDER BUILT CHILDREN

NO	AGE	sex	W L INDEX VARIATION IN PER CENT	WEIGHT	B M R. PER CENT	CALORIES PER HOUR
81	4	F		-30 0	+54.0	39 0
5a	4	F		- 74	143 0	
564	5	$\mathbf{F}$	-7	-21.0	+28.8	39 7
141	6	M	1	- 8.9	+29 0	49 0
558	G	М	-6	-15.3	+29 0	46.3
	G			-11 7	+25 1	467
491	6	M		-18 0	+81.0	60 7
448	6	м		- 30	+38.4	51.5
155	8	M	-5	-12 6	+38 0	47 5
406	8	$\mathbf{F}$		-21 0	+86.8	50.1
	0			-18.5	+25 7	51.7
72	8	$\mathbf{F}$	+8	- 87	+451	49.2
160a	8	M		- 95	+87.3	
340n	Ð	$\mathbf{F}$	<b>–</b> 5	- 1.8	+440	52.4
49	9	F	-1	-15 0	+64 B	5 5
87a.	10	$\mathbf{F}$	-8	- 59	+28 0	52 3
322	12	$\mathbf{r}$		-16 4	+200	03.8
412	16	$\mathbf{F}$	-1	-13.3	+24 0	68 5

The Width-Length Index variation shows relative breadth, or percentage broader or narrower than average, for the age, sex, group

Variation from average weight shows the percentage underweight referred to the Baldwin-Wood standard.

B.M.R. is the Basal Metabolic Rate referred to the Benedict Talbot scala.

B.M.H. In the Hamai Metabolic Rate reterred to the Benedict Impot scale.

aigns of hyperthyroidism, such as tremor, exophthalmus and other eye signs hyperhidrosis, and polyphagia. They were however high strung easily fatigued children and often had rapid pulses. The

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<sup>\*</sup>r equals the Pearson coefficient of correlation

"Statistics also show that there is a relation between the height and weight and the heart rate in children of the same age, in the sense that the heart rate tends to be slower in children of larger stature" This is shown in the accompanying table by Volkmann

RELATION OF HEART RATE TO BODY LENGTH AT DIFFERENT AGES (VOLKMANN)

YOK	SMALL CITILDREN	LARGE CHILDREN
1	146.5	128 1
2	124 0	111.0
8	113.2	104.3
4	111 7	110.2
5	106 0	102 3
6	102.5	90 9
~	101 0	93.8
8	97 0	98.0
9	0 00	89 0
10	93 0	88 0
11	88.5	8 0
12	91.3	81 0
18	87 6	81 0
14	89 7	89 a
15	81.0	81 0

Recent work<sup>2</sup> indicates that the normal body temperature is higher for young children than for adults. Dr. Stolz and Miss Ludwig at the Institute of Child Welfare. University of California, have studied variations in body temperature in healthy pre-school children. Rectal temperatures were taken at nine and eleven o clock in the morning and at one and three o'clock in the afternoon each day on 18 children. They reported that each child had his own range of temperature. In one child the average of all temperature readings was as high as 100° F and another as low as 99.2° F. The average for the total series of records was 99.5° F. which is distinctly higher than the rectal temperature of 98.96° F. which Howell reports as normal for healthy adults.

Jenkins' reported mean body temperatures taken at the time of basal metabolic rate determinations for 846 men to be 977° F, and for 2,408 women to be 981° F These were month temperatures, and are a little lower than Howell s' figures

Jenkins' material indicates that a 'rise of one degree Fahrenheit is equal to a rise in the basal rate of seven per cent in the case of men, or five per cent in the case of women. One degree Centigrade is the equivalent of twelve per cent for the men and nine per cent for the women. Dubois reports 72 per cent for each degree Fahrenheit or 13 per cent for each degree Centigrade.

Because the pulse rate is normally higher, and the body temperature is normally higher, at the vounger age levels, both of these facts seem logically in keeping with higher basal metabolic rates in young chil dren, since rapid pulse and wasteful rate of oxidation are associated with an overactive thyroid gland

Our findings would tend to agree in theory with Jenkins' basal pulse complex and with the prediction formula of Read,6 although to date we have not made use of these methods

The clinical application of these facts may be helpful in understanding a certain type of persistent low-grade febrile state which often reaches the pediatrician. After negative physical examinations, negative intradermal tuberculin tests, and negative roentgen studies, children with this complaint frequently remain under suspicion of obscure infection, usually pulmonary or hilar

Several observers' have reported a prepuberal rise in the basal metabolic rate. Inasmuch as our figures show basal rates much higher for preadolescent than for adolescent children, we wonder if the apparent prepuberal rise is not because the first observations were made at ages nine to ten instead of at ages five to six years. The averages of 1,334 first satisfactory basal rate determinations by age and sex for our 680 children are as follows.

	1	BOYS		GIRLS
AGES	NUMBER CASES	AVERAGE BASAL METABOLIC RATE	NUMBER CASES	AVFRAGE BASAL METABOLIC RATE
3-5	31	plus 16 91%	35	plus 11 42%
69	135	plus 10 71%	162	plus 853%
10-17	141	plus 025%	176	plus 2 58%

It will be seen that there is not only a prepuberal rise, but that there is a consistent and continual lise as the age level recedes to early child-hood

Consequently, it may be stated more accurately that the basal metabolic rate decreases regularly from early childhood to adolescence

# BASAL METABOLIC RATE VARIATIONS DURING ADOLESCENCE

The so-called distorted energy requirement of adolescent children is illustrated in the widely variant basal metabolic rates obtained during this period. The unusual activity and demands made by rapid growth is offered as explanation. Table V shows a serial study of basal metabolic rates on 26 of our adolescent children. Wide fluctuations in rate and rapid swinging from plus to minus or minus to plus were characteristic of this group.

Blunt, Tilt, McLaughlin and Gunn<sup>8</sup> studied 46 girls aged nine to eighteen years at yearly intervals. They state that neither the average figures for the different ages, nor the variation in their few individual girls showed any effect of puberty.

Gardiner and Brett<sup>o</sup> in a study of adolescent goiter compared physical measurements of one hundred cases of colloid goiter with average standards for height and weight. They reported that a large majority

TABLE II WIDE FLUCTUATIONS IN BABAL RATES DURING ADOLESCENCE ILLUSTRATE THE "DISTORTED ENERGY" REQUIREMENT

CASE NO	AGE	sex	W L INDEX VARIATION IN PER CENT	V \RIATION FROM AVERAGE WEIGHT IN PER CENT	B M R. PER CENT	CALORIES PER HOUR
290n	10-9 11-0 11-3 11-6	М	-6	-11.0 -10 0 -11 3 -10 8	+18 0 +25.9 + 4.5 +11 6	58 6 59 4 48 6 58 7
108	11-5 11-8 11-9 11-11 12-6 12-8 13-0 18-5	M	+1	- 0.3 -12 0 -12 0 -15 6 -16.3 -15 7 -17 0 11 4	+ 2 7 -21 0 +13.1 0 0 +21 9 +15 7 + 2.0 +11 6	56 0 45 7 47 0 54 7 68 4 04 1 59 0
5.38	11-9 12-4 12-7	М	+2	+13 7 +10 4 + 1.8	+23 8 - 9 0 -10	66 D 51 8 50 6
392	10-4 10-7 12-8 12-10	M	+0	+31.0 +10 4 +22 7 +23 5	-16.4 0 0 - 2 0 +15.5	46 0 51 4 66 0 57 8
437	12-0 12-6 18-0 18-0	И	+6	+11.1 00 00 + 4.5	-14 2 - 7 2 -21 0 - 6 4	46.5 51.5 45 4 57 8
403	11-0 11-4 13-0 14	И	-1	+14 8 +21.5 +21.2 +30 0	-10.2 -12 0 + 2.7 -10 7	48 0 48 1 59 6 58.0
546	9-5 9-8 9-11 10-8 11-1	М	-1	-12.5 -11 1 - 9 ° - 4 0 - 3 2	-16.9 + 5.5 - 5.7 +23.8 + 7.2	30.8 45 9 4° 9 60 7 53.2
44	0-0 10-0 10-1 10-4 11-4 11-7 11-10	F	-7	-25 0 - 7.2 - 7 7 - 5 1 -16 0 -11.0 -14.0	+21 7 + 4 0 - 4 7 -12.8 +2.0 + 5.5 +18 3	16 506 460 43.9 664 643
410	9-8 10-2 10-6 11-0 11-7 12-0	F	+2	+12.1 +10 9 + 7 0 + 5 0 + 9 6 +15 6	0 0 - 8.5 -18 0 0 0 +16 9 +11.8	51 0 49 0 41.8 50 8 60 7 58 4
410	11-1 11-7 12-7	F	+8	+40 0 +13 6 +24 5	- 8.2 + 1.0 + 7.1	48 4 52.3 56.9

The Width Length Index variation shows relative body width, or percentage broader or narrower than average, for the age, 82x, group.

Variation from average weight shows the percentage overweight or underweight referred to the Baildwin Wood height-weight table.

B.M.R. is the Bassi Metabolic Rate referred to the Benedict Talbot scale.

Benedict Hendry Baker and Aub Dubois standards were used for a few cases.

TABLE II-CONT'D

CASE	\GE	SEX	W L INDEX VARIATION IN FER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B M R. PER CENT	CALORIFS PFR HOUR
547	11- 12- 13-	F	-6	- 54 + 91 00	-20 8 + 9 1 +10 2	34 4 55 8 56 2
151	13-5 13-7 13-9 14-3	М	+5	+14 1 +10 4 +12 4 +10 0	+ 53 + 95 - 78 - 72	72 2 75 8 63 7 65 3
337	12-10 13-2 13-8 14-2	М	-8	-14 1 0 0 - 9 0 -13 7	-26 7 -29 0 -15 8 -10 8	40 0 43 0 50 4 54 5
202	12-2 12-8 13-0 13-6 14-0	М	-5	- 47 - 30 - 76 - 50 - 23	-11 S -13 1 +13 9 -13 0 0 0	47 6 48 1 64 6 52 6 63 7
389	11-10 12-1 12-3	М	+1	-10 0 - 3 6 - 3 0	+11 8 + 9 9 + 5 9	60 3 60 2 60 2
218	12-6 13-0 13-2 14-5	M	+3	+13 8 + 8 0 + 8 0 +12 7	± 13 -128 -180 + 26	52 2 47 4 57 3 61 6
246	10-2 10-8 11-0 11-11	F	-2	+ 9 0 + 2 0 - 6 6 - 8 6	- 50 +230 + 23 - 58	64 4 48 4 53 2
188	11-3 11-7 12-9	F	+2	- 86 - 76 - 36	+10 1 +11 3 -10 5	45° 471 381
56	10-3 11-4 12-0 12-1	F		+34 0 + 9 0 + 6 0 +10 8	-22 0 -23 0 + 2 0 + 3 2	54 4 55 5
253	10 11 12 13	F	47	+21 8 +30 0 +31 5 +22 8	+27 7 +18 3 - 9 2 -19 0	67 2 63 3 79 7 79 3
326	10-8 11-7 13-1	F	<b>+</b> 5	+18 0 0 0 - 5 8	+18 0 - 9 5 +15 1	53 6 43 7 57 7
332	10-S 11-0 11-6 11-9 12-6 13-0 13-5	F	+16	+23 0 +23 0 +27 1 +24 5 +23 8 + 8 0 + 4 4	-27 0 -19 0 +34 6 + 9 6 -18 4 +16 0 - 2 8	71 9 58 8 51 0 61 8 51 6
364	11-5 12-0 14-1 14-3	F	÷5	+ 5 2 + 3 7 - 5 0 - 5 9	+ 52 + 88 +269 +110	54 4 46 8 66 7 57 8

TARLE II-CONT D

CA8E \0.	AGE	8 <b>r</b> X	W L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B M.B. PKB CENT	CALORIES PER HOUR
3-2	10~2	F	-1	-11 1	-14.8	36.2
	10-0			- 3.8	+96	51.8
	11-0			- 21	-10 3	43.3
	11-3			- 0.3	-12.9	437
	11-0				~ 4.5	
181	10-2	F	-6	- 80	3.3	43.9
	10~9			- 90	+25 4	59.3
	11-4			- 57	+30 C	68 7
445	12-	F	-12	-17.2	+ 9.8	51.5
	13~			-12 5	+33.5	68 4
	13~			- 00	+71	55.1
	14~			-11.5	+28 1	65.9

of children with goiter were above average height for their age. Their hyperthyroid patients were below average weight for age and height. Their hypothyroid patients were above average weight for age and height.

Stocks, Stocks, and Larn's reported a similar finding with a possible explanation as follows "Gotter tends to appear more readily or to become more pronounced in relation to the child's size (in girls whose heights are above average for their ages) or girls whose thy roids enlarge about puberty tend in consequence to grow more rapidly in height." The authors incline toward the first explanation

Holmgren<sup>11</sup> in 1910 studied the growth spurt at puberty. He thought that rapid growth in height at the time of puberty was likely to produce a hyperthyroid reaction. In 1929 Thomas<sup>12</sup> stated that this conjunction of high metabolism with hyperthyroidism and rapid growth indicated that the thyroid hormone which stimulates metabolism was identical with the growth-accelerating hormone of the thyroid

#### FACTORS IN LOW BASAL METABOLISM

Fasting has been shown to lower the basal metabolic rate. Talbot s<sup>13</sup> study of fasting in cases of idiopathic convulsions in children in 1925, demonstrated definite reduction in metabolism. Schick and Cohen<sup>14</sup> the same year studied convalescent children and reported that a low basal metabolic rate followed the exhaustion of fevers and infections and might last from one to several weeks. They believed that the low pulse characteristic of early convalescence was caused by the low metabolism.

Since higher basal metabolic rates are characteristic and normal for voung children, all minus rates should receive careful attention as in dicating a deviation toward an abnormal glandular condition. Inspection of the mean basal metabolic rates for this series indicates that any minus rate in a preadolescent child is below the accepted limits of normal, when the correction factor of minus 11 5 per cent is applied

Examples are given in Table III where the basal rates when corrected with minus 115 per cent are all distinctly low

TABLE III
PREADOLESCENT CHILDREN WITH SLIGHTLY MINUS BASAL RATES

CASE NO	AGE	SEX	W L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B M R. PER CENT	CALORIES PER HOUR
279	6	F	+3	+ 4 ?	-3 6	34 5
258	7	$\mathbf{M}$	-3	+ 44	-13	42 7
128	9	$\mathbf{M}$	-3	+ 60	-2.8	44 3
115	8	$\mathbf{F}$	+4	+ 43	-20	39 6
100	9	$\mathbf{F}$	-5	+18 1	<del>-4</del> 1	41 2
101	4	$\mathbf{M}$		+11 6	-1 5	36 1
102	81	$\mathbf{F}$	-4	+ 50	-1 5	39 2
153	7	$\mathbf{F}$	+1	+ 42	-39	$45\ 2$
264	9	${f F}$	+1	+31 0	-40	49 5
295d	9	${f F}$		+17 0	-46	43 2
125a	8	$\mathbf{F}$	+4	+17 7	-24	45 4
498	7	${f F}$	+7	+109	-42	430
427	5	${f F}$	+2	+ 10	-36	31 9

The Width-Length Index variation shows relative breadth, or percentage broader or narrower than average for the age sex, group

Variation from average weight shows the percentage overweight referred to the Baldwin-Wood standard

B.M.R. is the Basal Metabolic Rate referred to the Benedict-Talbot standard

Children below ten years of age with basal metabolic rates no lower than minus three or minus four (Benedict-Talbot standard) tend to put on weight readily and to be sluggish. These show marked improvement with a little thyroid therapy

TABLE IV

LOW BASAL METABOLIC RATES IN BROAD-BUILT CHILDREN

CASE NO	AGE	SEX	W L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B M R. PER CENT	CALORIES PER HOUR
409	3	F	+10	+13 8	- 94	27 6
	4	_		+54 0	-23 3	30 9
				+27 0	11 0	33 3
	$\frac{4}{5}$			+32 7	-21 8	30 6
349	6	M	+1	+126	-23 7	32 5
331	Ğ	F	+1	+25 0	- 98	45 0
454a	6	$\tilde{\mathbf{F}}$	+2	+24 5	- 65	402
318	7	M	+4	+186	-19 4	40 7
45		F	+4	+200	- 48	430
10	8 8	-	1-	+110	0 0	406
543	8	$\mathbf{F}$		+28 0	- 71	46 6
154	9	M	-3	+28 7	<b>~25 4</b>	38 3
295b	10	M	+2	+28 8	~19 4	461
9	10	$\mathbf{F}$	+5	+18 8	-18 5	42 2
450	12	F	+12	+25 2	-26 0	56 5
506	13	F	LID	+481	-27 7	62 4
190	14	F	+13	+21 3	-196	56 5

The Width-Length Index variation shows relative breadth or percentage broader or narrower than average for the age, sex, group

Variation from average weight shows the percentage overweight referred to the Baldwin-Wood standard

B M.R. is the Basal Metabolic Rate referred to the Benedict-Talbot standard

Twenty eight of our cases in which the basal metabolic rate was very low were more overweight than the above group, and these children appeared with an entering complaint of obesity. Several of this group shown in Table IV were very broad built with large width length indices and all appeared to be markedly overweight. Their basal metabolic rates were low and became very low when corrected with minus 115 per cent. These children require thyroid treatment for a much longer period of time than the group in Table III, and need to stay on a restricted diet. They lose weight quite rendily while taking thyroid and most of them feel much better on thyroid than when not taking it. This group shows the extreme of the low variations and is close to the borderline of pathologic hypothyroid cases.

Very broad built children often have low basal metabolic rates and come in complaining of being overweight when they are not very much overweight for their build

#### ANOMALOUS LOW BASAL RATES IN SLENDLR UNDERWEIGHT CHILDREN

Dr Hoskins<sup>15</sup> of the neuro endocrine research department at Harvard reported "In addition to the sluggish, myxodematous type of deficiency as just described, there has come to be recognized in recent years

TABLE V

LOW BASAI METABOLIO RATES IN CERTAIN SLENDER BUILT CHILDRY

WHO ARE OPTEN ALLERGIO

MO.	AGE	BEX	IN DESCRIPTION IN PERCENT	VARIATION FROM AVERAGE TWEIGHT IN PER CENT	R. M R. PER CENT	CALORIES FEE HOUR
244	G	F	-7	-11.S	- 97	80 7
41	7	F	+1	- δ O	~ 76	259
558b	-	M	-1	-11.2	-11.3	36.6
107	8	F	-2	- 88	-19.3	28 8
874	8	Ж	+2	-11.8	-13.8	88 5
215	8	3.0		~ 78	-12 0	35 7
	ġ			- 21	~ 9.5	48.5
662	Ó	M		-17 8	~11.3	38.8
394	10	M		~ G.2	-20 7	39 5
20	11	F		-12.8	-17 0	85.5
0-6	11	M		-140	-12 7	48.1
99	12	F	+5	~ 3.5	-19.0	42.5
416	13	74	7	- 78	-12 5	53.5
80	16	М	-3	-17 8	-17 0	43 7
532	18	F	+2	-10 6	-18 7	45,2
	18			-10.1	- 34	50 f

The Width-Length Index variation shows relative breadth of body or percentage broader or narrower than aterage for the age asx group. Variation from average weight shows the percentage overweight referred to the Baldwin Wood standard.

R.M.R. is the Basal M tabolic Rate referred to the Benedict Talbot standard.

a thin, irritable nonmyxedematous type The subjects, far from being phlegmatic, are overresponsive to environmental annoyances. The causal relationship of thyroid deficiency to the condition is indicated

by the marked diminution of the basal metabolic rate and is proved by increase of weight and restored placidity of disposition under thyloid medication "

Topper and Mulier<sup>16</sup> reported a group corresponding to one of ours that was underweight with low basal metabolic rates

We have 67 cases showing moderately low basal metabolic rates in children, the majority of whom are slender-built and all of whom are under average weight referred to the Baldwin-Wood standards. These children might be expected to have high basal metabolic rates, both because of age and body build. Table V illustrates this group which deviates in the unexpected direction in basal metabolic rate. We have tried to find out what other things they share in common

As a group they are fairly quiet youngsters with a heightened upper respiratory susceptibility. A large proportion of them (46 out of 67) are also allergic. (Their upper respiratory susceptibility may be on an allergic basis.) Upon examination, allergy was the most suggestive common denominator. Consequently, a direct analysis of our allergic children for whom basal rates were available, was undertaken to demonstrate, if possible, any existent metabolic trend.

# BASAL RATES IN ALLERGIC CHILDREN

Out of a group of 72 allergic children, 58 had minus basal metabolic rates when corrected for age The other 14 ranged from plus 12 1 per cent to plus 18 per cent The average basal metabolic rate for the 72 was minus 58 per cent The tendency of the group therefore was toward low basal metabolic rates

Table VI shows the relationship between allergy and basal metabolic rate by age

TABLE VI

THE BASAL METABOLIC RATE IN 72 ALLERGIC CHILDREN 26 OF WHOM HAD MULTIPLE

MANIFESTATIONS

		AST	НИА		ECZ	EMA	н	AY :	FEVER	υ	RTI(	CARIA	,		INTES LLERGY
\GES	NO CABPS	NO B VI R	AVERAGE B N. B	NO CIBES	NO B VI R	IVPR (GE B M R.	VO C1818	NO B VI R.	AVBR (GF B M R	VO CASPS	NO B VI R.	AVPR (GE B M 12.	VO CIBES	40 B VI R	IVER (GE B M R
			minus			minus							_		
0 3	2	2	17 2% minus	1	1	19 9% plus			minus			plus			
46	16	25	4 9%	6	9	5 3%	6	11	81%	1		27 2%	]		
	1		minus			minus	1		minus			plus			plus
7 9	12	18	98%	4	5	16%	11	20	57%	6	9	4 0%	3	9	11 1%
			minus			plus	ŀ		plus			plus		_	plus
10 15	12	33	48%	4	9	13%	14	39	0.6%	2	5	10%	2	3	3 6%
Total			minus			minus			minus			plus			plus
	42		6 43%	15		4~22%	31		3 32%	9_		5 91%	5		81%

Presented by age groups and showing averages compiled from 198 B.M.R. determinations on allergic cases.

Not all of our allergic children were slender built with low basal metabolic rates. The babies with eczema were broader than average and for them metabolic studies are lacking

Measurements to classify body build were done on 97 allergic children. The younger children had more eczema and the older ones more asthma and hay fever See Table VII for the classification by age, sex and build

TABLE VII

BODY BUILD IN 97 ALLERGIC CHILDREN 23 OF WHOM HAD MULTIPLE MANIFESTATIONS

===										
AGES	NO	TIMA Average	KO	TEMA AVERAGE	10	FEVER AVERAGE	10	IOARIA AVERAGE	PENTAT.	ALLERGY AVERAGE
	CASES	BUILD	CABES	BUILD	CARES	BUILD	CARES	BUILD	CABES	BUILD
		3 0%		0 6%		1.0%		02%		16%
03	4	Narrow	9	Broad	2	Narrow	5	Broad	8	Broad
	Į.	3.5%	l l	1.3%	1	Functly		20%	i	20%
4 0	18	Narrow	1 7	Broad	7	Average	1	Broad	1	Brond
	i	2.0%	ļ.	0.5%	1	3.1%		87%		50%
79	11	Narrow	2	Broad	8	Narrow	4	Narrow	5	Narrow
	1	4.4%	{	07%	1	86%	[	11.0%	ì	07%
10-15	16	Narrow	3	Narrow	14	Narrow	1	Narrow	3	Broad
		8 4 %		0.5%		2.4%		21%		1.8%
Total	49	Narrow	21	Broad	31	Narrow	11	Narrow	10	Narrow

Presented by age groups and showing average body build in terms of percentage broader or narrower than the mean for age and real

The total allergic group averages ... 16 per cent narrow

Body measurements to distinguish build were recorded in terms of percentage broader or narrower than average for age and sex. The children with asthma and hay fever were consistently slender built with minus basal metabolic rates. Those with eczema were slightly broader than average and had variable basal rates. The children with urticaria and gastrointestinal allergy showed no consistent type of body build and their basal rates as a group ranged above average.

Whether there is a causal relationship between low basal metabolic rates and certain allergic tendencies in children is a question that merits further study. At the present time we can say only that in our group of slender built children with basal metabolic rates lower than average for their ages, and lower than average for their build 68 per cent were allergic. In addition to this 80 per cent of our allergic children, who had basal metabolic rate determinations done, had minus rates. Perhaps the constitutional factor in allergy is similar to the constitutional factor which causes the unexpected direction of variation in the basal metabolic rates.

Constitutional influences on basal metabolism are reported by the White House Conference to be

- 1 Those hereditary factors which affect body size and proportion
- 2 Those which affect nervous organization.

- 3 Those which produce a tendency to learness or fatness, aside from the endocrine functions
  - 4 The endocrine factors themselves

The report further points out that there are great varieties of body shape and size which possess normal endocrine functions and that

- 1 The presence of bone diminishes the metabolism per unit of mass while the presence of large amount of muscle increases it
- 2 A highly nervous or hysterical temperament accentuates the basal rate while a phlegmatic temperament lowers it

We have previously pointed out that broad-built children have larger bony frameworks than slender-built ones who have better muscles. Our personality and heredity studies have shown that, in general, our slender-built children are much more nervous, high-strung, and easily fatigued than our broad-built children, who are, in general, slower and more easy-going. All of these things are corroborative of the findings of the White House Conference Committee since our slender-built children consistently had higher basal rates than our broad-built ones, even though we had one group of slender children with low basal rates which were averaged with the other slender-built children

## CONCLUSIONS

- 1 A group study of any biologic data helps to establish trends in the general population and to diagnose normal variations for the individual
- 2 The individual case cannot illustrate all the elements that make up the group classification, nor can one case meet all the requirements that result in the conclusions drawn from a group study
- 3 Such a group study of 1,334 basal metabolic rates in 680 children shows every gradation from high to low rates
- 4 The basal metabolic rate decreases regularly from early child-hood to adolescence, where it reaches the adult level
- 5 Other physiologic data, such as pulse rate and body temperature, parallel the basal metabolic rate in its age level variations, tending to emphasize the reasonableness of the finding
- 6 High basal metabolic rates are characteristic of slender-built children regardless of age, and low rates are characteristic of broad-built ones
- 7 Since the higher basal metabolic rates are characteristic and normal for young children, all minus rates should receive careful attention as indicating a deviation toward an abnormal glandular condition
- 8 Children under ten years of age with slightly minus basal metabolic rates tend to put on weight readily and to be sluggish

9 In our group of slender built children with basal metabolic rates lower than average for their ages, and lower than average for their build, 68 per cent were allergie. In addition to this, 80 per cent of our allergic children, for whom there were basal metabolic determina tions had minus rates

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# MULTIPLE CONGENITAL RIB AND SPINAL DEFORMITIES

REPORT OF A CASE

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COMPARATIVELY little was known of rib and spinal anomalies prior to the development of roentgenology as a science and the widespread use of the x-ray in the diagnosis of bone conditions. It has become increasingly more evident that particular examples of congenital malformations of the skeleton are usually associated with other bone defects. For example, cases of absence of ribs are invariably associated with corresponding vertebral malformations.

Various congenital anomalies may occur in rib formation Among these anomalies may be mentioned

Cervical ribs
Variations in size and shape
Bifurcation
Fusion
Total absence of one or more ribs
Lumbar ribs

Cervical ribs have been known for centuries Galen (AD 200) men tions cervical ribs. Much has been written on this subject in recent years as many of the cases mentioned were discovered accidentally by x-ray

White states that of 5,728 chests examined with x-rays for various conditions other than anomalies, about 1 per cent showed congenital variations of all types. He states further that 20 cases of this series showed cervical ribs

Henderson<sup>3</sup> records 31 cases of cervical ribs in the routine examinations of approximately 80,000 patients. Eighteen of the 31 gave no subjective symptoms. Eleven of the 18 did not show a tumor and all had been subjected to an x-ray examination of the chest for some other reason question of tuberculosis, for large heart, for determination of possible substernal goiter, for possible aneurysm

Cushway and Maier<sup>4</sup> found 3 men with cervical ribs of 931 applicants whose spines were filmed routinely as a check-up for any possible abnormality before they were permitted to work as switchmen

From the Pediatric Service of the New York Nurser; and Child's Hospital

Because lumbar ribs are seldom of any clinical significance, the lit erature makes little of this anomaly. That they occur more often than is suspected can be deduced from the fact that Cushway and Maier report, in their series, 81 patients with ribs attached to the first lumbar vertebra as compared to 3 m whom the ribs were attached to the seventh cervical vertebra

Giles made 8.000 spine examinations and found 1,122 showing Seventy three of these 1,122 disclosed lumbar ribs.

Cummings reports a case of a rib arising from the transverse process of the third lumbar vertebra. The rib curved downward and fused with the transverse process of the fourth lumbar vertebra of the same This rib was discovered after an examination for pain in the back The rib was fractured as the result of miury

As to the variations in the sizes and shapes of ribs. White' found considerable variations in the size of the first rib Sometimes the first rib was almost as thin as a cervical rib. In other cases it was broad and failed to articulate with the sternum although the corresponding cartilage was completely calcified

Hrdlickar says that he found the third rib, particularly its sternal half more subject to modification and the eleventh and twelfth dif fering much more in size than in shape

Absent ribs have been reported by a number of observers. Steindler<sup>1</sup> gives a short résume of the literature on this condition and says. a distinction should be made between the partial defects of ribs and sternum which are comparatively common and the total de fects of one or more ribs which are extremely rare "

Sever examined several thousand films which had been taken of patients in the orthopedic department of the Children's Hospital in Boston and discovered a number of cases of absent ribs

There are not many examples of true bifurcation. Among these may be mentioned one by Bloomberg, who cites a case of a boy, four years old, who had bifurcations of the third and fourth ribs on the right side

Dennis10 cites 3 cases 2 of the fourth right rib and 1 of the third left.

Ruppricht11 discusses the case of a fetus in which he found bifurca tions of the third and fourth ribs both on the right side

Hrdlicka' found 6 specimens of forking of which only one specimen was on the left side. The sternal extremity was the part affected

Struthers12 describes 5 specimens and Adami12 3 These were all at the sternal extremity, mostly limited to the cartilage, and not very great in extent

Fused thoracic ribs are among the uncommon anomalies Hrdlicka examined 1,000 first ribs, 1,200 second ribs, and 14,000 ribs other than first and second Of this large series, there were 4 specimens of fusion He found 2 additional examples among ribs of American Indians This anomaly was on the left side in 5 out of the 6 In 2 of the 6, there was a junction of a cervical with the first rib, in 3, a junction of the first and second, and in 1, a junction of the third with the fourth rib In both cases of the union of the cervical rib with the first, and in one case of union of first with the second, the superior rib descended to fuse with the inferior one. The sternal part of these 3 specimens

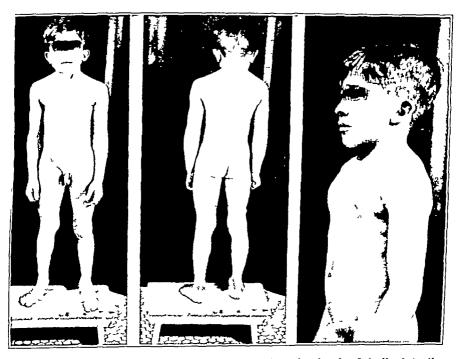


Fig 1—Photograph taken May 1933 Front view showing head inclined to the right and right shoulder higher than the left.

Fig. 2—Photograph of back taken May 1933, showing dorsal scollosis

Fig 3 -Side view Note bulging of right chest wall anteriorly

showed no abnormality In the remaining 3 specimens, the anomaly consisted "in an extension and more or less extended fusion of the neighboring borders of the ribs. In these cases we have seemingly a combination of a bicipital and bicaudal rib"

Meyer<sup>14</sup> presents a specimen showing fusion of the second and third ribs of the right side throughout three quarters of their length. He mentions other cases cited in the literature from which one may infer that the anomaly occurs most often between a cervical and a first, and less often between the ribs next in order of their sequence becoming extremely rare below the fourth rib. Indeed, Meyer tells

of only one case of fusion below the fourth rib and that, supposedly in a seven month-old fetus which was said to have been in the possession of Hunauld

Ruppricht<sup>15</sup> describes a fetus with union between the first and sec ond ribs on the left side. He found 57 cases of rudimentary first ribs in the literature from 1820 to 1926. In 21 of the 57 cases, there was some kind of union to the neighboring rib. The union was bony, car tilaginous or otherwise. He found a higher ratio of union when cervical ribs were present. In only 12 of all cases found was there a continuation with the sternum. Where the first rib was beyond the rudimentary stage, he found 7 cases of union between the first and

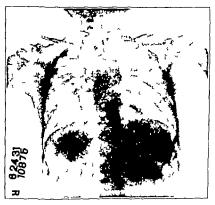


Fig 4—Roentgenogram of chest. There is a fusion of five ribs into a sort of bony plate in the middorsal region of the left side.

On the right side, there is a union of two three, or more ribs in the upper dorsal region and another union of two ribs below this.

second ribs In cases with fully developed ribs he found 3 instances oited, and he himself chanced upon 2 other specimens in the Vienna Institute of Pathology

Rees<sup>16</sup> examined a six year-old girl who had a congenital scollosis and found, among a number of bony defects a union between the second and third ribs on the right side

Gurney reported the case of a six year old girl who had what he describes ribs, many of them amalgamated at the back, two, and in one case three springing from the spine as one bone which separates into two (or three) about two inches from the middle line "

Hatch and Plume14 report a case of a seven year-old girl in whom

they found the sixth and seventh ribs fused for a short distance be youd their tubercles where the mass divided into four ribs varying in size

Sever's presents a number of children with very gross deformities, among which I could make out 8 to 10 well-defined cases of fusion below the fourth rib. In 1 case there was fusion between the ninth and tenth ribs, and in at least 4 cases there was a fusion of three or more ribs. In Sever's cases the anomaly was about equally divided between the right and left sides



Fig 5 —Roentgenogram of the spine in the cervicodorsal region Note the extensive spina bifida occulta and disorganization of the vertebral bodies.

## SPINAL ANOMALIES

Spinal anomalies have been reviewed, in recent years, by a number of authors. Danforth, in an interesting paper on numerical variations in vertebrae, contends that the vertebra is in a sense plastic and this character of the vertebra is largely a function of its position. To this may be added Cushway and Maier's statement that examination of the individual vertebrae in their series revealed an approximation to the so-called average vertebra though none were found identical "Each spine is characteristic of the individual, and he may be identified by a roentgenogram of the spine just as definitely as by a photograph of the face or by finger prints."

Willis,20 in a very interesting article, concludes as follows

- "1 The number of cervical vertebrae had been found practically constant not only in man but throughout the mammalian class
  - "2 The number of coccygeal segments is of negligible importance
- "3 The vertebrae may be divided into two main groups, presacral and sacral
- '4 Variation in the number of lumbar vertebrae is often coincident with, and compensated by, a reverse variation in the thoracic group. Likewise, at times, coincident with the lumbar variation a



Fig. 6—Roentgenogram of the lumbosacral region. There are six lumbar vertebras.

The sacrum is curved with convexity to the right. The first sacral segment shows a spina hifds occulta, a transverse process of the lumbar type on the right, and a lateral mass on the left.

reverse variation occurs in the number of sacral segments." With this in mind and also basing his opinion on the studies made by Todd<sup>21</sup> on the comparative evolution of the vertebral column in the mammalia, he found a presacral numerical stability of 95 8 per cent

Bohart<sup>22</sup> says Anomalies of the spine exist from statistics avail able in from 8 to 10 per cent of all persons examined.' This, of course includes all types of anomalies, both congenital and acquired

A consideration of congenital anomalies of the spine entails a long list of malformations For our present discussion, it will be necessary to give only a very brief outline of the more obscure conditions Among these we may consider

Spina bifida occulta
Variations in the body of the vertebra
Defect in the lamina
Congenital anomalies of the cervical spine
Numerical variations in the thoracolumbar region
Sacralization
Low lumbar, sacial, and coccygeal deformities

Spina bifida occulta is, by far, the most common congenital anomaly found in the spine. It may be found in any position of the vertebral column but more especially in the lower lumbar and sacial regions, the latter position being the most frequent site. Clinical manifestations do not necessarily accompany this deformity

Valiation in the formation of the vertebral body itself, is not common. The deformity may consist in a hemivertebia or otherwise malformed or displaced vertebra. When found in the thoracic region, one may expect some defect or abnormality in 11b formation. Thus, in the cases cited by Sevel and Rees, the thoracic spine showed this abnormality.

Incomplete union of the lamina is another deformity which is not common Willis found 428 per cent of skeletons with this deformity Cushway and Maier found only 2 cases in their series of roentgenograms in which the lamina was not united with the transverse process

Congenital anomalies of the cervical spine are uncommon. Especially rare are those described under the obscure term of Klippel-Feil syndrome. This consists in a numerical variation in the cervical vertebrae with more or less complete fusion into one mass, accompanied, in some cases, with spina bifida or other anomalies.<sup>23</sup>

Meisenbach<sup>24</sup> reports a case of total absence of the cervical spine in a girl ten years old

Reference has already been made to numerical variations in the thoracic and lumbar regions. This anomaly is much more frequent in the lumbar region than it is in the thoracic region, but as Giles puts it, an absent twelfth rib may give one the impression that he is dealing with six lumbar vertebrae when the reverse may be the case Giles found 50 cases with six lumbar vertebrae and 13 with four lumbar vertebrae. Cushway and Maier found 25 cases with six lumbar vertebrae, 6 with four lumbar vertebrae, and 5 with thirteen thoracic vertebrae. Each of the last 5 had thirteen ribs

Sacralization, or articulation between the transverse process of the fifth lumbar vertebra and the sacrum, is the most common congenital anomaly of the spine next to spina bifida occulta. There seems to be a great divergence of opinion as to the importance of this condition

and as to what does and what does not constitute true sacralization It will be sufficient for our purpose to say that there are many differ ent degrees of sacral transformation of the fifth lumbar vertebra. and that actual contact of bone, per se, may not give rise to symptoms The bilateral occurrence is more frequent than the unilateral

Coccygeal deformities are not painstakingly analyzed because most of them are of minor clinical significance and are usually considered along with sacral or other pelvic deformities

Anomalies of the fifth lumbar are common, and anomalies of the low lumbar and secrum are most common

There may be what is sometimes termed "asacralization" or 'lum barization," in which the uppermost part of the sacrum takes on the characteristics of a lumbar vertebra

Lastly there may be variation in the number of sacral segments or separation between them and accompanied by other associated mal formations

#### CASE REPORT

A white boy, five and a half years old was brought to the chair of the New York Nursery and Child's Hospital on June 24 1931 because he was stunted in growth. The only previous history in connection with the deformity was an asym metry in the chest wall which was first noticed when the child was two and a half venra old.

The father and mother were both in their twenties and well. There was one other child, a boy aged seven years, who was apparently of normal physical development. The remainder of the family history was essentially negative.

Examination disclosed a boy 37 inches in height and weighing 2914 pounds. He did not appear to be very strong and talked in a weak almost piping voice. He had much dental caries. His head was inclined to the right. There were two small papillomas anterior to the tragus of his right ear. The erns antihelicis and the antihelix of this car were sharply ridged. The right shoulder was higher than the left and a scoliosis was present. There was a bulging about the size of a plum in the midportion of the right chest wall anteriorly. There was a systolic murmur heard at the apex and at the pulmonic area but more pronounced at the latter

A roentgenogram of the chest disclosed the uppermost ribs so closely grouped on both sides that it was difficult to distinguish their individual outlines. Somewhat below this, on the left side, there was fusion of at least five ribs into a sort of bony plate. On the right side, there was one union of two three or more ribs and another of two ribs directly below this. The ribs on this side did not seem to be in contact with the spine. The lowest four ribs on the loft and the lowest three on the right appeared to be normal. The dorsal vertebrae, with the exception of the last three which were apparently normal, were of irregular shape and size and showed spina bifida occulta. There was also a scoliosis in this region with con verity to the right. The lumbar spine showed six vertebrae. The first sacral seg ment was asymmetrically developed and showed a lateral mass on the left side articulating with the flium and a transverse process of the lumbar type on the right, There was marked pelvic asymmetry with deviation of the distal sacral segments to the left. There was a spine bifide occulte of the first eneral segment. The in nominate bones were normal.

No abnormalities were found in the roentgenograms of the skull or long bones. A few months after the first visit, the patient left for the country, and we did

not hear from him until January, 1933

On Jan 23, 1933, his height was 411/4 inches and his weight 331/4 pounds Mantoux test with 0 02 milligrams of tuberculin resulted in a very strongly positive The mother later informed me that the child had frequently been in the company of a man who had since died of pulmonary tuberculosis No definite signs could be found in his chest and he was referred to the x ray department genogram of the lung fields was taken on Mar 15, 1933

The roentgenologist reported that the left hilum shadow appeared to be more dense and of nodular form This was diagnosed as adenopathy of the left hilum.

The child is now in school and the report from the teacher states that he is studious, his work is satisfactory, he is always neat and clean, and socially very amiable. He is well liked by the other children in the class

# SUMMARY AND CONCLUSIONS

An outline of some of the more obscure congenital abnormalities of the ribs and spine is presented. To this is added the report of a boy having unusual deformities of this character

The abnormalities discussed here can be correctly diagnosed only by x-ray or postmortem examination

Cervical ribs, although not uncommon, are not as frequent as lumbar

Total absence, bifurcation, and fusion may be listed among the rare congenital rib conditions

Spina bifida occulta is the most common finding and sacralization is next to it in frequency

Numerical variations in the thoracolumbar region are not rare lumbar vertebrae are found more often than four and both of these variations are more usual than thoracic variations

Variations in the body of the vertebia and defect in the lamina itself, are found less frequently

Absence of cervical vertebrae is rare Reference is made to a case of total absence of the cervical spine

The most common site for congenital spinal abnormalities is the lumbosacral region

A report is given of a boy having a congenital scoliosis and showing a peculiar type of fusion of ribs There are also extensive spina bifida occulta, irregularities in the vertebral bodies, and widespread sacral malformations

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2349 TWENTY SIXTH STREET

# VITAMIN D DEFICIENCY

# TETANY IN INFANTS WITHOUT RICKETS

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FIVE infants with tetany, unassociated with identification of rickets, are reported. That the tetany was dependent on a deficiency of ultraviolet radiant energy or vitamin D is evidenced by the prompt response to antirachitic therapy

The essential data are summarized in the table and the identification findings are illustrated in Fig 1. All infants received cow's milk in various dilutions during the hospital stay. One (Case 2) received 2 grams of calcium chloride during the first day of treatment. No calcium was given to any of the others.

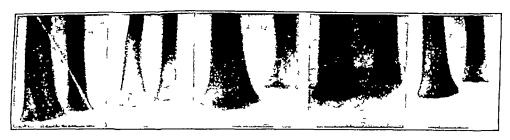


Fig 1 -Roentgenograms of five infants with tetany unassociated with rickets

In all 5 infants treatment with antirachitic agents resulted in a prompt and complete disappearance of symptoms and a return of the serum calcium and the electrical reactions to normal

A number of other infants have been observed with tetany but without roentgenologic evidence of rickets (24 out of 125 cases). They are not presented here because they either left the hospital before cure was complete, or the results of specific treatment were obscured by the administration of calcium in fairly large amounts

That a deficiency of sunlight or vitamin D may be present without rickets is suggested by the studies of Daniels¹ who found a striking improvement in the calcium and phosphorus retentions in seemingly normal infants following the addition of cod liver oil to the diet or the irradiation of the milk in the feeding. Swanson² noted a similar improvement in the phosphorus and calcium retentions in 2 infants with-

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THERAPOTIC RESULTS WITH ANTIRACHTIC AGENTS IN FIVE INFARTS WITH TEXANY AND VITHOUT BICKETS

1				T BEFORE T	BEFORE TREATMENT	APPER TR	APPER TREATMENT	DURATION OF
MUNBER	MUNBER MONTHS	SYMPTOMS	TREATMENT	SERUM CALC. (MG PER CENT)	BERUM PHOS.	SERUM CALC. SERUM PHOS. SERUM CALC. SERUM PHOS. (MG PER CENT) (MG PER CENT)	SERUM PHOS.	TREATURNT (DATS)
-	80	Convulsions, laryngo vspasm active facial C O C = 2.0*	Vigantol† Cod liver oil	6.5	E +	10.8	5.7	L
E1	14	Convulsions	Viorterol‡	7.0	9.4	+0	7.4	12
		0.00 = 40						
	16	Laryngospasm	Cod liver oil	7.7	3.0	0.0	1	20
-#	6	Convulsions, positive	Ultmviolet radiant	8.8	71	111	6.1	1
	_	C.O.C. = 48*	спетду					
IC.	153	Active facial, nystag Vigantolt	Vigantolt	0.7	8.2	10 @	6.3	18
		mus laryngospasm						
2	2	C O C Cathodal canada Call						

tVigantol is an unstantardized propri tary preparation of irradiated exposterol of high antirachitic potency tReceived I grams of exicium chloride during first day in hospital C. O. C. Cathodal opening contraction in milliamperes.

out roentgenologic evidence of rickets and with normal values for the serum calcium and phosphorus, following the addition of cod liver oil to the diet

### SUMMARY

- 1 Tetany in infants may occur without roentgenologic evidence of rickets
- 2 That this form of tetany is dependent on sunlight or vitamin D deficiency is evidenced by the prompt response to antirachitic therapy

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# ADVANTAGES OF STRAINED SOLIDS IN THE EARLY MONTHS OF INFANCY

# MANUEL M GLAZIER M.D BOSTON, MASS

DIFFERENCE of opinion still exists as to the best age at which to begin to feed cereals egg volk, strained fruits, and strained veg etables to a well baby. Morse, who represents the most conservative group, expressed the belief that cereal may be fed at the age of nine months, and advised a full diet at the age of one and a half to two years Hess<sup>2</sup> and Brennemann, on the other hand, say that from five to eight months is the proper age for a full diet. Brennemann believes that in troduction of solids into the infant's diet in comparatively early infancy (fifth and sixth months) is advantageous because the solids (1) contain vitamins, (2) have value in infant psychology, (3) are easily tolerated and (4) contain iron which is necessary. The earlier introduction of solids is not only advocated by most physicians but is practiced by most mothers.

The object of my study was to determine the best age at which to in troduce solids into the well baby's diet, and to observe whatever ad vantages or disadvantages were presented by the early introduction of solids

#### METHOD OF STUDY

A study was made of 231 infants who were observed in the Well Baby Clinics in the Reshndale District of the city of Boston in the years 1980 and 1931, and the first six months of 1982. This district contained for the most part, people of good social and hygienic surroundings, in moderate economic circumstances. The infants received medical care supported by nursing care from a group of well trained nurses connected with the clinic.

Solids were fed in the early months of infancy in such a way as to supplement the milk (breast or bottle) the infant got but not to complicate the feeding routine. This was done because too often mothers feed the infant as if he were a machine. For example the mother gives an infant one tempoonful of carrots, two tempoonfuls of spinach and seven ounces of milk. In this way she pays no attention to the natural power of selection of the infant, although the appetite of an infant will vary from day to day and from ment to ment I believe that an infant should be allowed some choice as to the amount and kind of food which he receives. This has scientific support, for in 1915 Ewvarde sllowed a group of hogs to select whatever they wished and as much as they wished from an assorted variety of basic food stuffs. The amount and type of food actually enton by the hogs was found best for their nutrition and development. Cowgill, in 1929, showed that dogs also are able

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to choose for themselves the optimum amounts of a complete food Davis, 8 9 in 1927 and in 1928, showed that this power of selection was correct in newly weaned normal, anemic, and rachitic infants

This natural power of selection of food by the infant was utilized in this study At all times the infant was allowed to take as much food as it wished. Bottle fed infants were prescribed formulas containing milk, water, and sugar (Mend's dextri maltose, Karo syrup, milk sugar, or cane sugar). Three teaspoonfuls of cod liver oil and three ounces of orange juice daily were prescribed (summer or winter) for every infant. Cod liver oil, however, was omitted during a hot spell or when ever the infant's appetite was impaired. The infants were seen once a week or once in two weeks, and the formula was changed as the indication arose.

When solids, such as fine wheat or barley cereal, were introduced into the infant's diet, the mother was instructed to teach the infint to swallow them an infant from two to four months old easily learned to swallow the well cooked and strained cereal that was softened with milk Occasionally, it took two weeks (twenty eight attempts) to teach a determined infant six to eight months of age to swallow solids. When the infant learned to take cereal, the mother was told to give it all it wished. As more cereal was taken, less sugar was included in the formula The cereal was given at 10 AM and 6 PM and was followed by bottle or breast After the infant learned to take cereal well, Zweibach, toast, egg yolk (cooked ten minutes), strained fruits, and strained vegetables were added to the diet teaspoonful of a new food was tried at one feeding and old foods could be mixed After the solids were eaten, the infant was allowed to take as much milk as it wanted The following rules were emphasized (1) boil everything the infant eats, (2) start only one new food a day, one teaspoonful at first, gradually increasing the amount, (3) give solids at the beginning of the feeding, (4) let the infant eat as much as it wants, (5) never force the infant to eat, and (6) if the infant refuses food, give water and orange juice until the next feeding time, and repeat this procedure until it is hungry

The full diet of solids was as follows (1) at 6 AM, milk (formula, whole milk, or breast milk), (2) at 8 AM, cod liver oil and orange juice, (3) at 10 AM, cereal or Zweibach, and milk, (4) at 2 PM, (a) broth or beef juice, (b) egg yolk, (c) potato, rice, or macaroni, (d) strained green vegetable (two of the following spinach, peas, string beans, stewed celery, carrots, squash, stewed tomatoes), and (e) milk, (5) at 6 PM, (a) cereal or Zweibach, (b) apple sauce, prune pulp, or strained apricots, and (c) milk, (6) at 10 PM, milk if the infant is awake. During the eighth, ninth, and tenth months, simple desserts, such as Jello, junket, and sherbet, prepared cereals, and strained meats were added to the dict.

# RESULTS

The 231 infants that were fed in the manner described were divided into four groups according to the age at which solids were first given Group I, during the second and third months, 38 infants, Group II,

TABLE I
WEIGHT IN RELATION TO SITTING HEIGHT

	NUMBER OF INFINTS	PFR CENT WITH WEIGHT WITH IN THE CALCULATED NORM N WFIGHT BANGE BASED ON SITTING HEIGHT
Group I	15	87
Group II	11	82

during the fourth month, 53 mfants Group III during the fifth and sixth months, 97 infants and Group IV, during the seventh eighth ninth and tenth months 43 infants. Each group was studied for (1) nutrition and development (2) effect on the gastrointestinal tract and (3) effect on food habits

TABLE II
WEIGHT (IN POUNDS) ACCORDING TO AGE

	RIETII	2 MO	4 110	6 ио	8 MO.	10 мо	1 YR.
Group I	7 -	10 6	14.5	17.5	20 0	21 7	23.8
Group II	7.5	10.3	14 0	16.8	192	21.1	22.7
Group III	75	108	13.5	168	19 1	20 6	22 0
Group IN	77	107	14 0	166	187	20 5	22.4

Nutrition and Development—Weight was regarded not only as a measure of the infant's nutrition but also in relation to the skeletal structure. For a number of infants observed in Groups I and II it was possible to record the so-called normal weight as calculated from the sitting height of the infant, 10 and to compare this normal weight with the actual weight of the infant. Thus, if certain groups show an unusual

Table III Development

	NUMBER OF INFANTS	DENTITION MONTHS	OKIAJAW TO BUIT BHTHOM
Group I	32	6.5	12.1
Group II	81	6 6	12.5
Group III	70	7.2	12.8
Croup IV	27	75	13 4

gain in weight, this gain in weight is desirable when it approximates the normal weight as calculated from the sitting height

Thirteen of the 15 infants in Group I and 9 of the 11 infants in Group II, whose calculated normal weights were recorded had actual weights within calculated normal limits (10 per cent) as shown in Table I.

In Groups I and II (solids given early) the yearly average gain in weight was respectively 0 9 and 0 7 pound greater than the weight gained in a year by infants of corresponding birth weight in Groups III and IV (solids given later)

The weight of each group is given in Table II

Dentition occurred earlier in the groups in which solids were introduced into the diet early as shown in Table III. Furthermore the age at dentition in Group I was one whole month earlier than in Group IV

There was also a definite relationship between early walking and early feeding of solids as shown in Table III. The infants in Group I started to walk at an average of 12.1 months, while the infants in Group IV started to walk at an average of 18.4 months.

Effect on the Gastrointestinal Tract—The solids were easily digested in all the groups, which included 166 infants. In the groups in which solids were given early there were fewer gastrointestinal disturbances associated with extraintestinal causes, and far fewer disturbances directly related to the gastrointestinal tract.

The first time stiained vegetables were given, whether early or late, most of them were observed in the stool without much digestion, and they colored the stool Carrots, beets, tomatoes, and string beans were well digested the second or third time they were eaten. Spinach required four to five attempts before it was digested to any appreciable degree

TABLE IV

EFFECT ON THE GASTROINTESTINAL TRACT

	NUMBER OF		CONSTIPATION	PRESENCE OF	GASTRIC DIS TURBANCES WITHOUT
	INFANTS	BEFORE DIET ADDED	AFTER DIET ADDED	GASTRIC DIS TURBANCES	EXTRA INTESTINAL CAUSES
Group II Group III Group IV	28 37 73 28	38 6% 37 9% 41 1% 53 5%	11 5% 10 8% 12 3% 32 1%	28 5% 29 7% 45 7% 32 1%	3 5% 5 4% 18 5% 17 9%

TABLE V

EFFECT ON FOOD HABITS

	NUMBER OF INFANTS	PRESENCE OF FAULTY HABITS	E\JOLMENT OF FOOD	PRESENCE OF FOOD DISLIKES
Group I	26	69 2%	93 0%	42 7%
Group II	37	43 3%	89 2%	35 1%
Group III	71	521%	77 0%	50.7%
Group IV	27	63 0%	77 7%	51 8%

In a few cases in which a wide variety of new cereals, vegetables, and fruits were tried within a few days an interesting syndrome developed. The infant took the foods well, was active, slept well, and had a bowel movement once or twice a day, which was brownish or the same color as the vegetables. There was no gain in weight and sometimes even a loss of one to two ounces for a week, but after this the gain was within normal limits.

When cereal was added to the diet, the character of the stool changed very little. In some cases the stool became softer and occurred twice a day instead of once. The addition of egg yolk to the diet gave the stool a golden brown color. In a few cases vomiting occurred, but this was due to egg-idiosyncrasy. When a bowel movement is soft, semisolid, ranging in color from yellow to brown, having very little odor, and occurring regularly once or twice a day, it is safe, as a rule, to say that the type of food ingested is proper.

The groups in which vegetables were given early showed a definite decrease in chronic constipation (Table IV). Constipation was present in about 40 per cent of the cases but the earlier a diet containing solids was given the fewer the cases of chronic constipation. Although 70 per cent of the constipated infants of less than seven months of age were relieved by the addition of solids only 40 per cent of the infants from seven to ten months of age were so relieved.

Effect on Food Habits—Each group was studied as follows (1) presence of faulty habits such as temper tantrums crying to be picked up wishing own way and difficulty in sleeping (2) enjoyment of food and (3) definite dislike of any food or foods.

The results (Table V) show that the groups fed solids early had better food habits and fewer food dislikes than those fed solids later Group I had 7 per cent more food dislikes than Group II, but in the presence of 26 per cent more faulty habits in Group I the result was not so striking since there is a tendency for food dislikes among infants with faulty habits.

Explanation of Results—A sufficient amount of vitamins and min erals is necessary for proper nutrition and development of an infant Frequently breast milk or formula milk does not fully supply this need even with the addition of average amounts of cod liver oil and orange juice. Apparently the reason why a full diet of solids is desirable is not that breast or bottle food does not contain the vitamins but rather that they are often contained in insufficient quantity.

A full diet of strained solid foods supplies an abundance of vitamins A B C and D. Such a diet gives an oversupply of vitamin A which may be stored in the body and used when needed thus increasing vigor and resistance to disease <sup>11</sup> Vitamin B is often deficient in either human or cow's milk. <sup>12</sup> <sup>13</sup> <sup>14</sup> <sup>15</sup> <sup>10</sup> The amount of vitamin C necessary to prevent searcy is only a fraction of the optimum amount needed. Vitamin D is particularly required in the metabolism of phosphorus and calcium <sup>17</sup> Wilson. <sup>18</sup> made roentgenographic examination of infants who had received cod liver oil and found rachitic changes in the bones of 97 per cent of those examined probably due to an inadequate amount of cod liver oil for Hess <sup>19</sup> believes that at least 15 cc of cod liver oil daily are necessary to supply the vitamin D content necessary to prevent rachitic changes in the average infant. The diet of strained vegetables possesses all of these vitamins in adequate quantities to effect proper development and nutrition for a normal infant.

Although cows milk and human milk contain all of the minerals necessary for development both are conspicuously deficient in iron Rapid growth and increased production of blood in the newborn infant<sup>20</sup>

depend upon a reserve of iron deposited in the liver. The liver of the newborn animal contains at least five times as much non as is found in the liver of the full-grown animal

Since milk is deficient in iron, one might expect the hemoglobin content of blood to be much higher at birth than in later infancy. William son, in 1916, proved this to be true. He showed that newborn infants average 23 2 gm of hemoglobin per 100 cc of blood, that by the end of the second month the hemoglobin drops to 18 3 gm, that by the end of the fifth month it drops to 13 7 gm, and that the drop continues until at the end of the twelfth month the hemoglobin is 12 5 gm per 100 cc of blood

The German investigators, Schwartz, Baer, and Weiser,<sup>22</sup> could not find, by histologic examination, any iron in the infant's liver or spleen after the fifth month. This means that all the iron stored in the newborn infant's liver is completely used up before the sixth month, and there after the infant is entirely dependent for iron on the intake of food Mayers<sup>23</sup> suggested that the drop in hemoglobin during the first year of the infant's life is a nutritional anemia, resulting from faulty feeding

The amount of iron required daily by an infant has not been de termined Morse<sup>24</sup> has expressed the belief that 0.5 mg of iron daily is sufficient for the first six months, and that 1.5 mg of iron daily is neces sary for the second six months. Larger amounts of iron, however, could well be used, for there is a definite relationship, within certain limits, between intake of iron and increase in hemoglobin. The addition of strained solid foods in the early months of infancy supplies a diet rich in iron and helps to prevent the nutritional anemia frequently present

The infants in my series showed definite ability to digest strained solids, even in the early months of infancy (second and third months). This easy digestibility may be due to the recent great improvement in the manufacture of strained fruits and vegetables. Caldwell, in his series of 60 infants, showed that strained vegetables were tolerated and digested at as early an age as six weeks. Introduction of cereal in the second month was not a radical step, for cereal is used to feed infants with pylotic spasm even during the early weeks of life. Strained vegetables when first fed the infant passed through the intestinal tract without any appreciable digestion. After two or three attempts the digestion of the strained vegetable was much improved. Apparently vegetables require certain digestive ferments to digest them. The production of these ferments, originally absent, seems to be stimulated by the ingestion of vegetables, with function soon following.

The "stationary weight" syndrome (failure to gain weight without other clinical evidence) followed the rapid introduction of many new strained solids. Apparently this was due to the metabolic change while the digestive ferments were being produced.

Constipation was present in about 4 of every 10 infants in the group of 166 studied, but the earlier the solids were given the fewer the cases of chronic constipation. Although 70 per cent of the constipated infants of less than seven months of age were relieved by the addition of solids, only 40 per cent of the infants from seven to ten months of age were so relieved. The reason for this beneficial effect in the early months is apparent Too small an amount of solids is an important cause for constipution. When this condition exists the mother gives the infant a laxative or a cathartic Repeated administration of these results in maladjustment of bowel mechanism so that the bowel muscles do not function until stimulated by a laxative and the result is a sing gish bowel (atonic constipation). When solids are introduced early in infancy there is a sufficient amount of total solids in the infant's diet thus eliminating the cause of atonic constination

The study showed that the groups fed solids in early infancy had bet ter food habits and fewer food dislikes than the groups fed solids in later infancy The explanation for this is that the longer the infant is on breast or bottle (without solids) the more accustomed it becomes to the milk (milk habit) and the harder it is for the infant to develop a liking for solids. The early feeding of solids stimulates a desire for a variety of foods and greatly aids in improving the infant's food habits.

#### CONCLUSIONS

A full diet of strained solids including strained vegetables given during the second and third months of infancy produces better nutrition and better food and bowel habits because (1) it contains adequate amounts of vitamins A B C and D (2) it contains iron that is needed to prevent nutritional anemia (3) it provides bulk to the stool, climi nating an important cause for constipation in infants and (4) it accustoms the infant to solid food early in life thus improving its food habits

I wish to thank the following persons for their cooperation Francis X, Mahoney M.D. Commissioner of Health City of Boston, Charles F Williasky M.D., Director of Well Bab: Clinics City of Boston, and Hazel Wedgewood, R. N. Director of Nursex, Health Department, City of Boston.

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### A CRITICAL CLINICAL STUDY OF VARIOUS INFANT FOODS

III FRESH WHOLE MILK MODIFICATION WITHOUT FAT DEFICIENCY

ADOLPH G DF SANCTIS M D JOHN DORSEY CRAIO, M.D AND
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NEW YORK N Y

I N A SERIES of articles of which this is the third we have examined clinically various infinit foods. This clinical study comprises a total of 259 cases, 149 of which were fed on whole milk modified by the method herein described and 100 of which were fed whole milk modified by a maltose and dextrin earbohydrate used as a control

The successful artificial feeding of infants consists in the adaptation of cow's nulk in such a manner that the two following conditions are fulfilled.

- 1 The nutritional needs must be supplied by the mixture as completely as possible
- 2 The formula must be adjusted so that it will be successfully toll erated by the digestive system and produce favorable digestive reactions.

The history of infant feeding is characterized by innumerable at tempts to meet these conditions in a satisfactory manner. The standards for the nutrational needs have become fault definitely fixed. It is obvious that the infant's needs are met by a formal amount of human milk of average composition. Based on a study of this natural supply and confirmed by records of successful artificial feeding it has been established that the average infant requires about 50 calories per pound of body weight daily conveyed in a fluid volume of about two and one half ounces, so that each ounce of food is valued at about 20 calories. This is the caloric concentration of human milk and may be assumed to be the correct physiologic standard. These calonies, of course, are provided by fat protein and carboly drate. Protein cannot be synthesized in the body and the needed amount of protein of proper quality must be supplied in the food given. Human milk provides in each two and one half ounces (50 enforce portion) about 10 gram of protein and this amount meets the needs of the miant per pound daily fact has been established that cow s milk protein is different in quality from that of human milk and, to compensate for this difference it is necessary to give the infant 15 grams of cows milk protein to be equivalent in nutritional value to the 10 gram taken in human milk. This amount of con's nulk protein is contained in 15 ounces of whole con a milk and is the accepted basis for the minimum con's milk need per pound for the artificially fed infant. To compound an adequate cow's milk formula for the infant it is therefore necessary to give daily,

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From the Pediatric Department of the New York Postgradunte Medical School of Columbia University

for each pound of body weight, 15 ounces of cow's milk diluted to two and one-half ounces with water and so reinforced by food additions that this volume will convey 50 calories. One and one-half ounces of cow's milk conveys 30 calones, so that 20 calones must be provided by the food additions These additional calonies can theoretically be sup plied by fat, carbohydiate, or protein, or any combination of these elements if calories only are to be considered, since they are fundamentally energy supplies However, since digestive conditions must also be taken into consideration, the distribution of these calories among the different food elements is of utmost importance. It is natural to turn at this point to human milk as a guide. Human mill contains over 3 per cent of fat and about 7 per cent of sugar, but less protein than this diluted cow's nulk. There seems to be little indication, there fore, for adding any extra protein to the mixture Moreover, cows milk protein in excess of the needs is not advantageous or even desirable Protein requires more energy expenditure for the process of digestion and the excietion of end-products, and an excess of protein in the food mixture affects digestive conditions in a manner which often proves undesirable, leading to constipation, putrefactive conditions, and high mineral excretion On the other hand, it seems of great significance that nature provides the infant with such a high proportion of fat pediatricians have always recognized this significance. Fat is of great importance as a source of the fat soluble vitamins. Fat aids the diges tion of protein and stimulates the proper assimilation of minerals, es pecially calcium. It also provides over twice as many calories per gram as does either carbohydiate or protein. Fat benefits digestion, and tends to control excessive fermentation and to keep the intestinal leactions well balanced, thus producing normal stools Accordingly, many attempts have been made to reinforce the fat content of cow's milk formulas so that it will compare favorably with that in human milk attempts were carried out by using top milk mixtures of such strength that the proportion of fat after dilution was similar to that in human milk, the remaining caloric deficiency being made up by carbohydrate It was found that many infants could not digest such a mixture successfully This failure was undoubtedly due to the fact that cow's milk fat is less easily digested by the infant than the fat of human milk, chiefly because the fat of cow's milk occurs in large tough globules Accordingly, the attempt to supply any considerable part of the needed additional calories in whole milk dilutions in the form of fat was largely abandoned, and the general procedure in artificial feeding was to provide rather more than the minimum amount of whole cow's milk and to make up the caloric deficiency by carbohydrate alone, being perforce satisfied to give only the amount of fat conveved by the amount of whole milk used Since infants can usually tolerate more fresh cow's milk fat than that supplied by the minimum need for cow's milk, as determined by the protein requirement, this procedure permitted the use of formulas which supplied from one half to three-quarters as much fat as would be supplied by human milk. Such mixtures were found to be quite generally tolerated by average healthy infants. It was always recognized that the proportions of fat, carbohydrate, and protein differed markedly from Nature s guide, human milk, and that the mixture was, therefore, not ideal, but, since a consideration of the digestive tolerance is equally as important as the provision of a theoretically correct mixture of ingredients thus compromise was accepted as necessary

In the meanwhile, the advance of scientific knowledge presented in creasing evidence of the beneficial effects of generous fat in the diet In the meanwhile, also the advance of scientific knowledge has shown the way to meet this fat need without disturbing digestion. It is well known that the difficulty which the infant demonstrates in digesting raw cow's milk fat tends to disappear when the milk is processed in any way Concentrated milks have long been recognized to be much more readily digested than fresh milk. The introduction and increasing use of dried milk and dried milk products have proved that infants have little difficulty in digesting the milk fat of milk which has been dried especially if homogenization has been introduced into the process of manufacture Definite proof of this is the marked success achieved in the use of several dried modified milks now generally in use able physicians have found that infants can successfully telerate and thrive exceptionally well on feedings containing 3 to 35 per cent of processed milk fat

The inference is obvious. If enough fresh raw cow's milk fat cannot be successfully added to a fresh milk dilution so that the mixture simulates human milk in proportions of fat carbohydrate, and protein, and it infants can successfully tolerate increased amounts of processed milk fat the addition of processed milk fat rather than fresh milk fat is certainly indicated.

A milk modifier which embraces these principles has therefore been devised. Instead of consisting as do the commonly used milk modifiers, of carbohydrate alone, this modifier consists of a muxture of processed cows milk fat, mixed easily digested carbohydrates a small amount of protein, and a significant amount of mineral salts, especially iron. By using this modifier, it becomes possible to add to the desired min imum of fresh cow's milk the needed additional calories partly as fat and partly as carbohydrate. The final mixture therefore, approaches more nearly to the proportion of food ingredients found in human milk than has ever been possible to achieve by the use of usual modifiers but does not overstep the infant's fat tolerance, since the fat addition is the easily digested processed homogenized milk fat.

It was shown earlier that the basis of proper feeding for the artificially fed infant was a minimum of 1.5 ounces of cow's milk made up to a volume of 2.5 ounces with water To this there was to be added enough ad ditional food to provide 20 more calories, making a total of 50 calories for

each 25 ounces of mixture If carbohydrate alone is added to supply this deficiency, it is necessary to add about 5 grams of carbohydrate. The resulting percentage composition of such a formula would be

Formula A —Cow's milk, 15 ounces, water, 1 ounce, carbohydrate, 5 grams

Fat	20%
Carbohy drate	87%
Protein	18%

These proportions are vastly different from those found in human milk, and the mixture is so high in carbohydrate that some infants would show evidence of the carbohydrate tolerance being exceeded. In many instances, therefore, the added calories are supplied partly by increasing the amount of cow's milk and partly by added carbohydrate, as for example

Formula B—Minimum milk, 15 ounce, added milk, ½ ounce, water, ½ ounce, carbohy drate, 25 grams

Fat	28%
Carbohydiate	67%
Protem	25%

Such formulas are usually well tolerated, although some infants find difficulty in handling so much fresh milk fat and the balance of food elements is far from that in human milk

With this new modifier, 4 grams are added to the basic mixture of 15 ounces of cow's milk with 1 ounce of water. The resulting formula has a percentage composition as follows

Formula C-1 ounce of whole milk, 1 ounce of water, 4 grams modifier

Fat	31%
Carbohydrate	59%
Protein	21%

The mixture approaches the composition of human milk, the fat being very similar in amount. The protein is necessarily higher and the carbohy drate is therefore lower in proportion. Since only 60 per cent of the fat supplied in such a mixture is raw cow's milk fat, while 40 per cent is processed fat, it is possible for the infant to take this relatively high proportion of fat without digestive disturbance. The digestive conditions on such a feeding should approach those of infants on breast milk feeding.

The relation of the food elements to each other in the different formulas explained above is readily seen in Table I, which gives the proportions of fat, earbohydrate, and protein in the total solids of the formulas

TABLE T

PER CENT OF TOTAL BOLIDS	HUMAN	FORMULA A (1.5 OZ. MILK, 1 OZ. WATER 5 GR. CARBO- HYDRATE)	FORMULA B (2 0 OZ. MILK 0 5 OZ. WATER, 2.5 GR. CAEBO HYDRATE)	FORMULA O (15 OZ. MILK, 1 OZ. WATER, 4 OR. MODI FIER USED IN THIS STUDY)
Fat	80.5	10 0	23 4	28 0
Carboliydrate	56.5	69 0	56.8	53.2
Protein	13 0	14.4	20.8	18.8

In addition to providing the infant with sufficient calories, water, protein, fat and carbohydrate it is necessary to consider carefully the supply of minerals and vitamins. Any formula which provides enough cow s milk to meet the protein needs adequately convers milk salts in amounts greater than those provided by human milk. Cow s milk con tams three and one-half times as much mineral matter as does human milk with the individual mineral constituents in approximately the same relation to the total ash, iron being the only marked exception Accordingly, a dilution of 15 ounces of cow s milk to 25 ounces with water will still provide over twice as much mineral matter as 25 oz. of human milk. The use of this modifier further augments this supply because of the appreciable amount of milk salts contained in it only specific numeral substance whose content in cow s milk compares unfavorably with that in human milk is iron. Even in human milk the amount of iron provided for the infant is questionably adequate, while cow s milk is notably deficient in this element. Accordingly this modifier has been reinforced in iron content to that a formula in which it is used contains three times as much iron as a corresponding one made with the ordinarily used carbohydrates.

Whole cow's milk provides a vitamin supply fairly comparable to that in human milk. Dilution of course diminishes this supply especially in regard to the fat-soluble vitamins A and D. This modifier by rendering the net fat content of the formula similar to that of human milk tends to compensate for this loss of dilution insuring a vitamin supply similar to that of whole cow's milk. The supply of water-soluble vitamin B in a formula using this modifier exceeds that of ordinary milk formulas. This is due to the fact that it is made partly from malted whole wheat grain by a process which retains to a large extent the original vitamins of the grain. Whole wheat is known to be one of the richest sources of vitamin B. This additional supply of Vitamin B so of undoubted benefit to the infant. Vitamin B stimulates appetite and growth. Vitamin C as always in infant feeding, must be provided by dietary additions of fruit juice.

In brief this modifier used with dilutions of whole cow's milk makes it possible to offer to the infant, formulas which contain generous protein mineral salts and vitamins, with increased supply of iron and vitamin B and with a generous supply of easily digested fat similar

each 25 ounces of mixture. If carbohydrate alone is added to supply this deficiency, it is necessary to add about 5 grams of carbohydrate. The resulting percentage composition of such a formula would be

Formula A —Cow's milk, 15 ounces, water, 1 ounce, carbohydrate, 5 grams

Fat	20%
Carbohy drate	87%
Protein	1.8%

These proportions are vastly different from those found in human milk, and the mixture is so high in carbohydrate that some infants would show evidence of the carbohydrate tolerance being exceeded. In many instances, therefore, the added calories are supplied partly by increasing the amount of cow's milk and partly by added carbohydrate, as for example

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The mineral elements in the ash of the modifier are approximately as follows

Potassium	0296%
Sodium	0 596%
Calcium	0 210%
Magnesium	0 079%
Iron	0 0036%
Sulphur	0 140%
Phosphorus	0 160%
Chlorine	0 135%

The caloric value of the dry powder is 5 calories per gram or 150 calories per ounce, or expressed in spoonfuls

- 1 level teaspoonful of modifier dry, or 17 grams-85 cal
- 1 level tablespoonful of modifier dry, or 5 grams-25 cal
- 1 ounce by weight-18 level tenspoonfuls or 6 level tablespoonfuls.

The eurd tension of various formulas made with milk, water and modifier used in this study has varied from 3.9 to 12.7

#### CLINICAL STUDY

The clinical study of this modifier was divided into two groups the first group consisting of 99 cases using milk water and added modifier. The fat infants over four months of age received from 40 to 45 calories per pound body weight, the average infants under four months of age and moderately thin infants of any age were given from 50 to 55 calories per pound body weight, and babies underweight for age were given 60 to 65 calories per pound body weight. In the 99 cases in this group, the modifier was added as a carbohydrate would be added the babies under ten pounds in weight getting 120 calories per day in the form of modifier and the babies over ten pounds in weight getting 180 calories. Table II shows the results of this group

#### TABLE II

=====

Number of infants on modifier	99
Youngest infant put on modifier	2.0 weeks of ago
Average ago of infants put on modifier	25 months
Minimum length of time on modifier	00 weeks
Average length of time on modifier	166 weeks
Maximum length of time on modifier	".5 months
Average weekly gain per infant	5.21 ounces
Number of digestive disturbances	~ (g.08%)

Of the seven digestive disorders above mentioned one was in the form of anorexia and six of diarrhea two of which had an associated anorexia

As the caloric value of a tablespoonful of this modifier is 25, 8 to 9 tablespoonfuls per day were eventually given to all infants. The one case of anorexia occurred when the modifier was increased to 9

tablespoonfuls and corrected when this was reduced to 7 The cases of diarrhea were all of the fermentative type, having 5 to 7 yellow to given semisolid stools a day. Five of the 6 cases occurred when the formula contained 9 tablespoonfuls of the modifier and the remaining one when 8 were used. All the stools returned to normal in from three to five days by the simple removal of the modifier.

Each of the gastiointestinal upsets was very carefully studied. It occurred to us that it would be possible to reduce the percentage of fresh cow's milk fat and increase the processed fat by a readjustment of the formulas. With this in view, a series of formulas (Table III) were calculated. These show that by a reduction of the amount of fresh cow's milk and by an increase in the amount of the modifier, the percentage of processed fat could be increased. Fifty infants were fed according to the formulas in Table III. The number of gastrointestinal upsets were, however, approximately the same in both groups. Nevertheless, the average gain in weight was considerably higher in the second group, and we believe that the best results with this modifier will be obtained by following the method as outlined in Table III

The difference in feeding in this manner from that used in the first group is best explained by sample cases

Baby J D, aged three months, weight 12 pounds Assuming that this baby requires 50 calonies per pound body weight, the total calonic requirement would be 600

Formula of First Group

Milk 21 ounces Water 10 ounces

Modifier 1½ ounces (approximately 8 table-spoonfuls)

Formula of Second Group

Milk 19 ounces Water 14 ounces

Modifier 10 tablespoonfuls

In a five-and-a-half-month-old baby, weighing 14½ pounds, requiring 725 calories a day, the difference in methods of feeding is still more clearly brought out

Formula of First Group

Milk 27 ounces Water 10 ounces

Modifier 8 or 9 tablespoonfuls

Formula of Second Group

Milk 23 ounces Water 12 ounces

Modifier 11½ tablespoonfuls

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"The amount of modifier added hereases the volume of daily formula by about 1 or.
This table allows at least 15 gr protein per its body wt. At no time until the eighth month is the raw fat as high as 40 per cent of the total.
The dighth and ninth month formula pare the way to whole milk.

### TABLE IV

Number of babies on modifier	50
Loungest infant put on modifier	1 35 months
Average length of time on modifier Maximum length of time on modifier Vinimum length of time on modifier	11 months 6 weeks
Average weekly gain per infant	5 62 oz
Number of digestive disturbances	4 (8%)

Of the four digestive disturbances mentioned two were in the form of anorexia and two of diarrhea. The cases of anorexia occurred when the infants were on 11 and 12 tablespoonfuls of the modifier, respectively, the condition was corrected by simple reduction of the amount of modifier. The two cases of diarrhea were fermentative in type, there being from 5 to 7 vellow to green semisolid to watery stools a day, one infant had excorrated buttocks. Both cases occurred when the babies were receiving 11 tablespoonfuls of the modifier. By elimination of the modifier from the formula the stools became normal in from three to five days.

A group of 100 cases was used as a control These infants were fed a mixture of fresh cow's milk, water, and a maltose dextrin carbo hydrate. The results in this group are shown in Table V

#### TABLE V

Number of control cases	100
Youngest baby to which mixture was given	2 weeks
Average age at which mixture was started	2 months
Minimum length of time on feeding	6 weeks
Average length of time on carbohydrate	21 weeks
Maximum length of time on carbohydrate	9 months
Average weekly gain per case	58 ounces
Number of digestive disturbances	7 (7%)

Of the seven digestive disorders one was in the form of anorexia and six of dialihea, two of which had an associated anorexia

The anorexia occurred on a formula containing 1½ ounces of carbo hydrate and was corrected by simple reduction of this element. All of the cases of diarrher occurred on a formula containing 1½ ounces of the carbohydate and were fermentative in type, consisting of from 5 to 7 green to yellow semisolid to watery stools a day. On the removal of the carbohydrate and giving a formula of one half milk and two-thirds water the diarrhea cleared in from three to four days.

#### COMMENT

In analyzing the results of the first group one finds of significance the average weekly gain of 5.21 ounces and percentage of gastiointestinal upsets of 6.9 per cent. In the second group we find a weekly gain of 5.62 ounces and an incidence of gastrointestinal upsets of 8 per cent.

The obvious conclusion is that Group II did better than Group I in weight gain, however, the incidence of intestinal upsets was about the same. This shows as previously mentioned the superiority of feeding this modifier as designated in the formulas of Table III, rather than using the modifier as a carbohy drate would be used. The difference in results in the two groups is due apparently to the fact that the modifier changes both the fat and carbohydrate element of the formula and a greater percentage of processed fat is available which is apparently more digestible. The method of modifying in the second group more nearly approaches the percentage contents of human milk.

In the third or control group of babies fed with a carbohydrate modifier the average weekly gain was 58 ounces and the meidence of digestive upsets 7 per cent. These results compare favorably with the results in Group II

In general, it may be said that the results in feeding infants by the method of modification herein described compare favorably in weight gain with a control group of cases fed commonly used mixtures of milk, water, and carbohydrate. By using this modifier it becomes possible to add to the desired minimum of fresh cow's milk, the needed additional calories, partly as fat and partly as carbohydrate. The final mixture approaches more nearly to the proportion of food ingredients found in human milk. In addition the modifier has been reinforced in iron content so that the eventual formula contains approximately three times as much iron as is found ordinarily in milk formulas. Vitamins A and B are also found in greater quantities than in the commonly used milk mixtures.

With the use of sufficient antiscorbutic agents no manifestations of scurvy occurred

The ordinarily used antirachitic agents were employed, and there was no greater incidence of rickets in these series of cases than in similar groups of cases reported.

#### TABLE IV

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# COMMENT

In analyzing the results of the first group one finds of significance the average weekly gain of 521 ounces and percentage of gastrointestinal upsets of 69 per cent. In the second group we find a weekly gain of 562 ounces and an incidence of gastrointestinal upsets of 8 per cent

76 histories, to which series he has added 2 cases from personal observation. Hunt's has discussed in detail the clinical and pathologic features of the disorder. Both papers are supplemented with bibliog raphies covering the entire period since Lucas's in 1883 first reported an instance of late rickets accompanied by albuminuma. We desire to report the following case of renal dwarfism now under observation in the Children's Division of the National Jewish Hospital at Denver

M. K., femule, born March 8, 1820 at Tueson, Arizona. Admitted to our hospital, February 12, 1933 The reason for admission was given as extreme mal untrition and exposure to tuberculosis. The father is alive and well, as are two sisters, ages seventeen and eighteen years respectively. The mother, aged thirty



Fig 1.-X ray picture of wrists, showing normal development.

nine years, born of Jowish parentage in Russia, came to America at the age of one year. In 1991 she moved from Illinois to Amona because of tuberculosis of the right sacroline joint. Five or six years age she became a morphise nddiet. The mother a history further disclosed that for nine years prior to the birth of the patient she had not menstruated and that she had submitted to at least two xray exposures with the probable object of inducing abortion. Recent examination of the mother revealed extensive healed pulmonary tuberculosis and active tuber calous of the sacroline joint

The baby was born through ecsarcan section during the eighth month and weighed 3 pounds, but by the tenth day the weight had decreased to 1½ pounds. In the absence of breast milk, artificial feeding was necessary. There is a wage history of convulsive sciences at intervals during the first two years of life. Eruption of the first tooth took place before the fourth month, but a diagnosis of nekets was made shortly afterward. For the past two years the patient has given little anxiety except through her autonishing failure of physical and mental development.

m 32 cases as five years and two months, and so many develop the syndrome at puberty that it is frequently known as the rickets of adolescence Lathrop maintains that roentgenograms may be consistently negative for rickets in well-defined cases, and others consider the skeletal changes as quite independent of that disease

### SUMMARY AND CONCLUSION

A case of renal dwarfism with some unusual aspects is presented Whether the kidney affection is of prenatal origin or was developed The retaidation in growth and after birth cannot be determined development has been so proportionate and the congenital changes have been so inconspicuous that congenital mactivity of the gonads or other endocrine structures need not be seriously considered, particularly in the absence of neoplastic invasion

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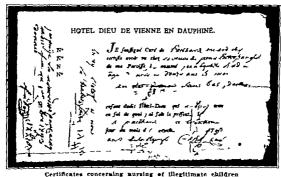
- 3 Lucas Lancet 1 993, 1883 4 Lathrop Am J Dis Child 18 612, 1926

#### ANTIQUES OF PEDIATRIC INTEREST

# T G H DRAKE, MB FRCP(C)

IN THE first certificate, dated February 4 1780, the Rectours of the General Hospital of Saint Laprit and St Jacques of the city of Marscelles, certify that one Maric Chaix is nourishing and rearing in her home an illegitimate child, aged seven years, who was placed at





nurse by that hospital and in whose registers are entered particulars of the child. The second document certifies to the Hotel-Dieu of Vienne in Dauphiny that the village priest of Pailhard has visited an illegitimate child, aged about twelve years and four months, pertaining to that hospital, who was being cared for by a widow, and that the child was in good health at the time—October, 1793 Marginally, the priest asks that material and not finished clothing be sent, and the secretary of the hospital notes that he has paid the nurse for five months the sum of  $17\frac{1}{2}$  livies, an amount equivalent in present-day purchasing power to about 70 French france

Through experience the French hospitals had found that it was cheaper to place infants with nurses in their own homes than to attempt to rear them in the hospitals

The payment for nursing varied with the age of the child. The first year, while the infant was being wet nursed, was the dealest, the nurse's fee usually remained at a somewhat lower rate from the second to the seventh year, and from the eighth to the twelfth year the fee depended on the amount of work the child was able to perform. In addition to money payments, some hospitals clothed the child until the end of its fourth year, and others until the end of the seventh year.

Schedules of wet nursing fees at various times, taken from various sources, are as follows

In 1717, a Bourgeois of Viens records in his diary the payment of 3 livies (francs) per month for the wet nuising of his daughter in the nuise's home

In her diary, the daughter of a Conseiller of the parliament of Paris writes that in 1747 she paid 9 livres, in 1754, 8 livres, and in 1760, 6 livres per month for the wet nursing of three successive children in the nurse's own home

In 1802, in reply to a letter of enquiry from the mayor of Angers, the mayor of a neighboring town states that their schedule of fees for wet nursing is 5½ francs per month from birth to the age of two years, and from that time on 4¾ francs per month

In 1823, the city of Paris paid the wet nurses 7 francs per month for the first year of the child's life, 6 francs during the second year, 5 francs from the third to the sixth year, and 4 francs from that time until the twelfth year

In 1834 in France, the total cost of rearing a child in the care of a wet nurse from birth to its twelfth veir varied in different districts from 800 to 1,300 francs

A bill from the "Grand Bureau de Nourrices sui Lieux, fondé en 1825 par Mme Quost," dated Paris, 1880, itemizes a wet nursing account thus

> For the nurse's first month 40 francs For the expenses of transporting the infant 30 francs The bureau's fee 7 francs

# Critical Review

#### DISORDERS OF INTERNAL GLAND SECRETION IN CHILDREN

FRITZ B TALBUT M D BOSTON, MASS

THE review last year presented in as simple form as possible the reviewer's interpretation of the pertinent facts then known. Since then, several significant articles have appeared and out of the enveloping for some very definite landmarks and lighthouses have material

ized to help the searcher for truth to steer his course

Although many records of basal metabolic tests appear in the literature it is unfortunate that their value is greatly reduced and perhaps entirely cancelled because the records give only the heat production in terms of 'per square meter of body surface' and fail to give the total heat production. To make matters worse the metabolism per unit of body surface is recorded in deviation per cent without stating what formula is used to obtain the surface area of the body or what stand ands the metabolism of the subject varies from. The reviewer makes a plea that all records of basal metabolism always should record the total heat production. A brief review of the present practice in in terpreting the metabolism of childhood appeared in the July 1933, Czerny Festschrift issue of this Journal

It has not been possible to discuss the basal metabolism data in the reported endoorine cases because it is only recorded in plus or minus per cent. The reviewer had the privilege of seeing the original data of some of the important cases reported and found that the data as presented led to quite a different picture of the progress of the discase when the metabolism was charted in terms of total heat production and compared with the expected heat production for the height and

for the weight

#### THE INTERRELATION OF GLANDS

One is impressed on reading the endocrine literature by the number of papers which still publish beneficial results from the use of this or that gland extract in polyglandular syndromes. Since accurate diagnosis of such conditions is not yet possible in most cases such reports should be considered with healthy but reasonable skepticism. Aub says in his Presidential Address before the Association for the Study of Internal Secretions in 1932. "In recent years at many clinical meetings the inhibitic point of view in regard to treatment has been actively championed. This point of view did much good by eliminating that which was false and unproved and an intelligent skepticism is always most valuable but the reaction has gone too far."

Evidence has accumulated which shows the intimate interrelation

of the endocrine glands Cushing savs, "Out of all the present welter of discovery relating to the internal secretions it becomes increasingly evident that the pituitary gland holds a dominating position in the endocrine series and evereises direct or indirect control over an

unsuspected number of brochemical processes of utmost importance to the economy of the body and should one venture to single out, from many, those particular steps that in recent years did most to accelerate our progress, they were the discovery in the anterior lobe of the two inseparable hormones of growth and sex "These will be referred to again in the section discussing the pituitary gland

Thy oid Gland—Since endemic goiter is attributable to a diminished or deficient supply of rodine, it has come to be considered as a deficiency disease—a deficiency of rodine. It has been recently shown that the hyperplasia which represents a stage of rodine deficiency can be brought about in animals, at least by diets rich in either calcium chloride or sodium chloride. The practical inference is that where rodine is lacking and cannot be replaced thy rold hypertrophy would be increased by the liberal use of chlorides in the diet. Salt should there fore be used sparingly by persons with rodine deficiency.

Hupothyroidism - Recently attention has again been drawn to the work of Mason, Hunt and Hurythal13 who found mainly on adult subjects with hypothyroidism and a low basal metabolic rate, that when the blood cholesterol was higher than 200 milligrams per cent they were benefited by thyroid medication Bronstein studied twenty-five normal children and found the average cholesterol values 190 milligrams per He found an increased cholesterol of 277 to 782 milligrams per cent in twelve children with hypothyroidism These values were lowered On the other hand the literature cites numerous by thyroid therapy cases with hyperthyloidism in which a low cholesterol was not present despite a very high basal metabolic rate. Since abnormal cholesterol figures are reported in other conditions independent of the rate of heat production these findings should be held under advisement until further data are available. The reviewer depends on the clinical findings plus the rate of metabolism in the diagnosis and treatment of hypothyroidism of children

Hypothyroidism without myvedema is commencing to attract attention in the literature. Yournans and Rivania have described in adults a group of symptoms which they think should suggest this condition, viz constipation nervousness poor emotional control lack of energy, vague pains localized in various regions. These patients also have a low metabolism. If the symptoms and metabolism respond to thyroid therapy, the patient falls in the group of hypothyroidism with out myvedema. If not the low metabolism is due to some other physiologic process. The reviewer has reported briefly a similar group found in girls, principally between the ages of fifteen and seventeen years with more obscure symptoms but with definitely low metabolism according to our present standards, who were markedly benefited by the use of thyroid. They are still being studied to determine exactly where they belong in the scheme of disorders of metabolism

Pituitary Gland —According to many authorities the pituitary gland holds a "dominating position" in the endocrine series. It is known to contain separate hormones of growth and sex and the recent work of Evans also reports an adrenalotrophic hormone and a hormone which influences the sugar metabolism—a lactogenic hormone, and a thy reotrophic hormone. The significance of these new hormones to human life will not be clear until more is known about them. Cushing draws attention to gross and microscopic changes which result from "withdrawal or increase of the two principal hypophyseal hormones sepa-

rately "Prompt shrinkage takes place in the gonads, the adrenal cortex and thyroid after hypophyseal extirpation in the dog and rat, while hyperplasia follows injection of the growth hormones. Since the clinical effects of chromophobe adenoma are comparable to the former laboratory experiment one finds atrophy of the same glands in this condition and in acromegaly (hyperpituitarism) there is a cor responding hyperplasia.

Although an active growth hormone has been prepared, it is not yet available for clinical practice nor is it certain that it will give universally good results comparable to those seen in animals. "None of the commercial preparations which are supposed to be active 'contain more than traces of growth promoting substances even when extracted and injected into suitable animals." Harvey Cushing s classical article on dyspituitarism and Tracy Putnam's presentation of the present status of diseases of the hypophysis both should be read in the original. They are quoted freely in this review.

The human hypophysis (pituitary) consists of two lobes, the anterior and posterior. Cushing prefers to call the anterior lobe the adenohypophysis and the posterior lobe the neurohypophysis according to the terminology of Berbleinger. This terminology will be followed here

The neurohypophysis is the site of the formation of pituitrin. Dain age of this part of the pituitary does not cause diabetes insipidus. This symptom comes from injury to the hypothalamus and with it may be associated obesity gonadal atrophy and somnolence. It is difficult to understand why this is so, since the polyuria characteristic of diabetes insipidus is promptly relieved by the injection of pituitrin

The symptoms of obesity gonadal atrophy and less frequently som nolence which are frequently called Frohlich's syndrome can be produced by injury to the hypothalamus at the sex hormone is known to be in the adenohypophysis. This is another inconsistency which needs explanation. Attwell' after a critical study of the literature concluded that Frohlich's syndrome is not a disease of the pituitary.—the adenohypophysis—results in genital atrophy or infantilism. Tumors do not arise in the neurohypophysis.

All the diseases of the adenohypophysis are so far as is now known, due to one of three kinds of tumors—chromophobe adenoma acido philic adenoma, and basophilic adenoma. The chromophobe adenoma secretes no hormone and the symptoms of hypopituitarism resulting from it are due solely to destruction of the normal glandular elements by pressure. The acidophilic adenoma is responsible for the growth hormone oversecretion of which causes gigantism and acromegally. The basophilic adenoma is rare and may secrete the sex principle. These adenomas may be associated with abdominal obesity impotence or amenorrhea glycosuria, hypertension and fractures in their later stages. Hirsutism may or may not be present.

Chromophobe Adonoma — The symptoms due solely to new growth and pressure are characteristic of chromophobe adenomas but do not appear until the later stages of acidophilic or basophilic adenomas. These tumors differ, therefore in that the former has no symptoms at first, while the latter have initial symptoms due to excessive secretion

of their individual hormones. In the later stages when pressure and destruction take place, the symptoms of all three are affected accordingly. With increasing extension of pressure, the optic chiasm which hes above the hypophysis becomes involved, causing limited fields of vision and eventually blindness. Further afield, the hypothalamus when involved causes the train of symptoms connected with it. If sight becomes impaired, operation is necessary to preserve vision. Cushing has found on removal of the soft expanding chromophobe adenoma that the relief of pressure on the surviving normal gland substance has in some cases allowed the resumption of normal function.

Acidophilic Adenoma causes gigantism so long as the epiphyses are open and acromegaly results after they are closed. The giant reported by Behrens and Barra is a boy who at thirteen and one-half years attained a height of seven feet four inches (2215 cm). If this type of adenoma progresses to a size which compresses the normal gland substance, sex and other functions will be interfered with X-ray has been used with presumable success on this type of tumor by Cushing. This treatment has not yet been used in a large enough number of cases to evaluate its importance. At this writing, it gives hope of a rational method of procedure in a disease which previously had no treatment.

Basophilic Adenoma—Although the sex hormone may originate in the basophilic cells, there is evidence that it might come from elsewhere This question will have to be settled before a clear picture of all the activities of the hypophysis can be obtained. Cushing's' description of the basophilic adenoma, however, has made a picture which the clinician can readily recognize. Since very few cases are recorded in the literature, it is not possible to say if this is a disease characteristic of childhood. The youngest recorded case was fifteen years old. The disease is characterized by adiposity which spares the extremities, hypertension, impotence or amenorrhea, and fractures. Hypertension is also found in hyperplasia of the adrenal cortex and other conditions. It may be contrasted with the lowered blood pressure found in hypopituitarism of chromophobe adenoma.

The obesity of hypopituitarism does not yield to any known extract of the hypophysis? Kenyon reports successful treatment of these types of obese cases by regulation of the diet. 12

The Lawrence Moon-Biedl Syndrome was reviewed by Reilly and Lisser 16. It is characterized by dystrophia adiposogenitalis, atypical retinitis pigmentosa, mental deficiency familial occurrence and skele tal abnormalities, most frequently polydactylism and syndactylism. The writers emphasize that this disease "necessitates family occurrence." They thought two of their patients improved with endocrine therapy.

Parathyroid Glands—The parathyroids supply a hormone which regulates the supply of calcium in the circulating blood and influences the phosphorus level. Complete destruction of the gland results in tetans and death unless the calcium level is maintained either by the administration of calcium or a potent extract of the parathyroid gland (parathormone of Collip)

From the clinical point of view acute tetany is rapidly relieved by calcium chloride, but when it is due to hypoparathyroidism the cause

of this symptom is not reached without the use of parathermone. This hormone should be used with care as its desage has not been completely established for all ages of childhood.

Hyperparathyroidism (Von Recklinghauson's Disease Osteitis Fibrosa Cystica Generalisata)—This condition has been critically reviewed from the pathologic point of view by Jaffe 11. The article deserves careful reading by anyone interested

The symptoms consist of pain bone tenderness deformity tumor and spontaneous fractures of the bones. Polvuria and polydipsia are present in most cases. Associated with the increased urinary output are hypercalcium and hyperphosphatum. This results in decreased muscle tone constipation and depressed feelings. Sometimes a para thyroid tumor can be detected by the physician but it is surprising how often this observation is lacking in the recorded cases. This is probably due to the small size of some of the tumors. The disease is usually first suspected by the x-ray findings and the diagnosis is made from the chemical examination of the blood

Albright¹ has summed up the results obtained on ten cases from whom parathyroid tumors had been removed and seventy three cases from the literature. He finds that the amount of circulating calcium and phosphorus is extraordinarily constant. In the adult the calcium range is 95 to 115 milligrams and the phosphorus 38 to 45 milligrams. This constancy is made possible by drawing on the calcium and phosphorus reserve in the skeleton when these salts are lowered in the circulating blood and redepositing any excess when the salt content becomes too high. The skeleton acts in this way as a reserve station which keeps the circulating calcium and phosphorus constant. The serum calcium may be as high as 13 milligrams and the phosphorus as low as 3 milligrams in a characteristic case.

Demineralization of the skeleton may involve practically the entire skeleton but changes are most pronounced in certain bones or bony parts. The long tubular bones show the greatest degree of change and these are closely followed in frequency by the spine sacrum, pelvis skull, jaw bones and thoracic flat bones. The teeth are not affected

Albright found a relationship between hyperparathyroidism and kidney stones as well as secondary kidney changes simulating Bright's disease. When a positive diagnosis of hyperparathyroidism is made and confirmed by the chemical laboratory the tumor should be sought by the surgeon until it is found. If the chemical laboratory says that it is not hyperparathyroidism that is the final word despite clinical symptoms

Adrenal Gland -The adrenal medulla seems to be intimately connected with heat loss from the body 17

Adrenal Cortex—Since the isolation of the hormone cortin (Swingle Pfiffer and Hartman) and the demonstration of its dramatic effect on Addison's disease a large number of physiologic investigations have appeared in the literature. The adrenal cortex is essential to life. When it is destroyed there is an extreme fall in body tempera ture, a marked loss of weight in dogs come by injections of cortical extract.

Tumors of the adrenal are often malignant adenomas. The charac teristic symptoms are hypertension, hypertrichosis, deviations of the

secondary sex characteristics such as masculinization of women Tumors are sometimes associated with precocious sexual development and pseudohermaphroditism, especially in the female

Although advenal insufficiency is raiely seen in young children, the possible applications in the future to pediatric problems justify a brief discussion of it here Haitman says that in contical insufficiency asthema develops insidiously and is the first symptom to appear weakness was shown to be due to involvement of the muscular tissue The circulation soon becomes involved and in later stages the heart action may be feeble and the blood pressure low function of the kidney becomes weakened and fails metabolism is lowered and can be brought back to normal by the administration of cortin, it cannot be raised above normal level by this hormone Cortin is essential for growth and when absent the resistance to toxins is diminished. It apparently has some beneficial action on Vitamin B and C Pigmentation of the skin, as is seen in Addison's disease, seems to be due to lack of contin and to be benefited by its administration In adrenal insufficiency the blood sugar is frequently Hartman also has reported a new hormone called "cortilactin" which influences the secretion of milk in rats

The data given above is confusing for the practicing physician but is of extreme interest to the physiologist. Today this knowledge has no practical bearing on pediatric problems, but it has opened a door which promises many possibilities for the future.

Sex Glands—Novak and Long<sup>14</sup> made a survey of the tumors of the sex glands and found that granulosa cell tumors of the ovary have a feminizing tendency due to the production of folliculin Arrheno blastomas have a determining tendency

The ovary is activated by the sex hormone of the adenohypophysis thus stimulating the maturation of the gradian follicle. This starts the ovarian hormone called theelin by Doisy—folliculin or estrin by others. Theelin therefore, favors menstruation. Progestin (corpornlutin) is then formed to stimulate the growth of the endometrium during the second half of the menstrual cycle. Theelin then inhibits the sex secretion of the adenohypophysis and menstruation takes place. Theelin is apparently now available in physiologically active preparations and progestin is not

Prolan is found in the blood and urine of pregnant women ("Aschleim and Zondek's Test for Pregnancy")

Although it has been shown that there is a definite interrelation of the various glands in the endocrine system, it is not clear in most cases just what that relation is. Attempted therapeutics would be simplified enormously if one could answer the old and simple conundrum "which came first, the hen or the egg?". As in other fields of medicine the best results can only be obtained by correcting the cause Little can be said for treating the symptom alone. It seems probable that as knowledge progresses to the point where the secondary effects of primary glandular overaction or underaction are completely understood that the term "polyglandular syndrome," as it is used today will disappear from the literature and be forgotten as are the miasmas of the past

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# American Academy of Pediatrics

# Proceedings

# THIRD ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

Monday Afternoon Session June 12, 1933

# Round Table Conference on Blood Disorders Characterized by Bleeding

Leader Dr Thomas B Cooley Assistant Dr Heyworth N Sanford

The meeting was called to order at 2 PM by the Chairman, Dr Thomas B Cooley, Detroit

DR COOLEY—We cannot cover all the disorders of the blood in any one round table discussion. Last year we talked about the anemias of infancy. This year we are going to take up the disorders associated with bleeding. It is not our idea to try to tell you all about the subject. What we want to do is to lay out a framework for discussion and have you all join in

There seems to be no very good name for this group of disorders. They are sometimes spoken of as "hemorrhagic diatheses," but that is not a particularly good expression. I like the German name better— Blutungsubel "It seems to express our meaning better than any term in common use with us

Of course, not all of these diseases are, strictly speaking, disorders of the blood, but when we are considering the hemorrhagic disorders, though they have widely differing etiologies, the resemblances in symptomatology make it simpler to group them together

Any consideration of the bleeding disorders requires some conception of the blood clotting mechanism, which is so often involved in hemorrhagic states. I shall try first to lay some foundation for discussion of that process

The ideas about the clotting mechanism are, as you know, still quite confused There are plenty of theories as to how clotting takes place, but the problem is not settled and some of the theories are quite contradictory. Some are complicated and hard to understand. The reason for the multiplicity of theories as doubtless that we have not yet sufficiently accurate methods for studying many of the questions involved. Problems of colloid chemistry and physicochemistry are encountered which are still not very well understood and not susceptible of convincing demonstration by present methods.

The principal differences in the theories depend on whether the clotting process is looked upon as a series of chemical reactions, or a group of physicochemical phenomena, or a combination of these two, or whether there is a ferment action or something analogous to it involved. There also is not complete agreement as to observed facts, and there are some generally recognized facts not explained

by any of the theories Some of the theories are too elaborate to attempt to go into in a meeting of this kind

Shown on the slide is what one might call the classic theory in its simplest form. It is quite generally agreed I think that as I have shown in the chart on the slide, there are present in the blood as it circulates prothrombin, calcium and fibrinogen, and probably a small amount of the lipid cophalin and that the fluidity of this mixture is maintain 1 by something for which we may use the term antithrombin without too great citainty as to its precise nature

When the blood is shed, changes take place which are represented on the lower part of the slide and which probably are started by the disintegration of the platelets. We agree that they contain explain probably an additional amount of prothrombin, and therefore add the c to the hed blood as compared with the circulating blood. The clot the fibrin formation itself is almost universally agreed to be due to a combination of thrombin and fibringen. Whether this is an actual chemical reaction or whether it is a physicochemical adsorption process is another matter. The classic theory in its simplest form is that when blood is shed the platelets become agglutinated and undergo disintegration with the hieration of cephalin, which in the presence of calcium (probably serving as a catalyst) converts prothrombin to thrombin. Thrombin and fibringen unite to form fibrin which is deposited as a network of long needles emmeshing the corpuscles. Ultimately this mass of fibrin needles and corpuscles contracts, producing the firm clot and extrading the serum.

This diagram does not show some of the more recent developments of this theory, such as the formation of an inert 'metathrombin by a union of thrombin and antithrombin and some other anticongulant reactions which Howell has brought out. It is the emphasis put upon the anticoagulants that chiefly distinguishes Howell a ideas of clotting from those of some other workers. His theories would make a very complicated diagram and at present they are hardly sufficiently proved to have important clinical application. It is fairly clear, how ever, that there must be in the blood one or more substances having an anti coagulant action and that serve to keep the blood in fluid form during its course in the circulation. How one may suppose they exert that action must depend on whether one accepts the idea of the clotting process as a train of purely chemi cal reactions including chemical neutralization of the anticongulant factors by products of platelot disintegration or whether one agrees with the physicochemi cal explanation of the upsetting of the delicate equilibrium of a balanced colloid complex by the introduction of the new factors introduced from the platelets.

Bordet has been one of the important workers in the study of clotting and his theory deserves mention. (Slide) He makes use of a different terminology derived from the old idea of congulation as a ferment action, though he does not subscribe to that idea. For prothrombin and cephalin he uses the terms—servayme' and 'cytoxyme,' and thinks they unite in the presence of calcium to form thrombin. He lars especial stress on contact of the blood with a foreign surface in the wound (or in the test tube)—The importance of this contact is unquestionable and is the reason for the use of paraffined tubes in the laboratory to minimize clotting. He postulates a 'proserozyme which in our terminology would be pro-prothrombin,'' which in contact with a foreign surface in the presence of cal cium becomes serozyme then serozyme and cytozyme form thrombin which unites with fibrinogen to form fibrus

Mills, of the University of Cincinvati has busied himself with the clotting problems for a long time, and has taken up and developed the ideas of the Eng lishman Wooldridge. He is a careful worker, and I think deserves attention, though his theories seem not to have gained much acceptance.

(Slide) He believes that two independent clotting processes go on at the same time. The clotting is inaugurated by a direct combination of what he calls tissue fibrinogen with the blood fibrinogen. Tissue fibrinogen is supposed to be a combination of cephalin with varying proportions of protein, and to be derived both from platelets and from tissue juices. The union of tissue fibrinogen and blood fibrinogen he believes can happen directly without any of the preliminary reactions of the classic theory, and the production of small amounts of fibrin in that way sets off the classic mechanism

The classic theory as I presented it in the first slide seems to be the one commonly accepted in this country, and is as good as any for the interpretation of clinical phenomena

I suppose most of you have seen articles by Kugelmass regarding his idea of measuring increased or decreased coagulability of the blood by means of a "clot ting index '' He seems to have been a pupil of Bordet's, and has done a good deal of work in New York on this question of measuring coagulability, both as a diagnostic procedure and as a preoperative precaution. He derives what he calls a clotting index by taking the product of the factors which favor clot forma tion and dividing by the anticoagulant factor, antithrombin (Slide) The nor mal prothrombin index is given an arbitrary value of one. The fibringen index is five tenths, because that is not an arbitrary value. It represents the ratio of the refractive power of the serum to that of the plasma, which is normally one half The prothrombin index is the relation of the prothrombin time in a particu lar blood to that of a normal control All theories agree in assigning to the platelets the most important place in initiating the clotting process measures the platelet value by taking 200,000 as the normal count, and 50 per cent as normal disintegration in one hour, thus getting a normal figure of 100,000 for active platelets, to which he assigns a value of one in his index. The antithrombin, again, is given a normal index of one I shall not go into the methods of determining these values, which are to be found in laboratory manuals values assigned give a normal index of five tenths, from which Kugelmass allows a variation of two tenths as within normal range

This scheme is, I think, rather a good one—not so important in the diagnosis of the marked disorders as in minor things, such as the tendency to oozing after a tonsil operation, tooth extraction, or something of that kind. Here is a sample of how it works out (Slide) This was a hemophilic patient. The prothrombin index was 0.44, fibrinogen, 0.5, platelet lysis 10 per cent (index 0.2), antithrombin index 1.2. The clotting index is 0.036. The clotting time of the patient's blood was thirty minutes. Kugelmass emphasizes the very great lowering of the clotting index in hemophilia as compared with almost any other condition. It is evident, however, that in thrombocytopenic purpura with a very low plate let count the index will be fully as low.

With this rather sketchy background of the clotting mechanism, I wish to say some things about hemophilia Dr Sanford is to talk of some of the other disorders

You all know that hemophilia is the great example of hereditary disease. It is also an example of sex linked heredity, never transmitted direct by the male, but through the daughters of the male to their male offspring. Or, it may go through two or more female generations and finally appear in male descendants.

(Slide) Here is a rather simple family tree of a hemophilic family, in which you may see how these things go For instance, you will see in one of the lines of female descent how the trait has gone through two female generations to be come manifest finally in their male descendants. This does not show some of the things that Dr Birch speaks of, and that I have not seen mentioned elsewhere

I should be interested to study enough hemophilic trees to see how well her statements are justified. She says the study of hemophilic trees seems to show that hemophilic males tend to have more female children, and their daughters to have more males, and that the chances are that about two out of three of these male descendants will be hemophilic. That cams to me, on theoretic grounds, rather doubtful, and I should like to see it demonstrated.

The question is always coming up whether there is any possibility, according to the laws of heredity, of hemophilic ever being transmitted by the hemophilic male to his own sons, or whether on the other hand, there is any possibility of a female hemophilic. Apparently, so far as our present ideas of hereditary transmission are concerned, there is no possibility of the male transmitting hemophilic directly. There seems to be a remote possibility of the female hemophilic. That it has not been definitely proved to occur has been neseribed to the fact that it would involve a union of two hemophilic strains, and that the bleeding tendency in that ease would be so marked that the child probably would not be born alive. This may be a plausible explanation.

Though hemophilia is not a common lisease its clinical features are quite fa miliar The tendency to prolonged bleeding from slight trauma is the most strik ing feature, and it may be observed very early in life. There are on record plenty of cases of fatal bleeding from circumcision in hemophilic families, enough so that it has been necessary to make regulations to prevent it. The tendency to bleeding from minor trauma is not usually observed in early infancy, probably because infants are not often subjected to trauma, but it does appear fairly early in life. While it is the most common symptom of hemophilia, it is not the only characteristic type of blooding Bleeding into a muscle without definite trauma beyond some slight muscle strain is, for instance not an uncommon feature Perhaps the most striking thing in long time observation of hemophilies in the clinic is that nearly all of them in time have joint hemorrhages. First one sees them with the ordinary bleeding from trauma, and presently one finds them developing hemarthresis in one or another joint, and this is a progressive thin, with repented homorrhage and increasing deformity of the joint so that in any hemophilic family one is fairly sure to find several cripples of this type

One of the most troublesome features of the clinical picture is the tendency to bleeding from the gums. Whether the had tooth which nearly all hemophilic children have are to be ascribed to mainutrition from lack of propor exercise I do not know, but certainly their teeth are had and they tend to produce hemor rhage by wounding the gums. One of the difficulties in the handling of hemophilis is the had teeth, the obvious need for their removal, and the danger of sover bileeding from the ordinary dental operations. This is perhaps the most troublesome thing in the handling of the hemophilic child in the clinic. We have at present no satisfactory method of meeting this problem, and it is a question whether to let the teeth go and have the gums subject to bleeding from traum or to have the teeth removed and take the chance of dangerous hemorrhage.

I need not tell you that these hemorrhages are not only serious, but quite often fatal. It is not so very uncommon to read in the paper of a child bleeding to death from hemophilic hemorrhage, or being ill for a long period. Just the other day I noticed that one of the children in the family of the King of Spain, (as you know that is one of the hemophilic families) had been for ten days or two weeks in the hospital with bleeding which was still making trouble. The hemorrhage does not ordinarily tend to stop spontaneously until the process of repair of the wound is complete. They are not stopped by clotting. When an apparently, fit is something like trying to make glue adhere to a wet surface.

(Slide) He believes that two independent clotting processes go on at the same time. The clotting is inaugurated by a direct combination of what he calls tissue fibrinogen with the blood fibrinogen. Tissue fibrinogen is supposed to be a combination of cephalin with varying proportions of protein, and to be derived both from platelets and from tissue juices. The union of tissue fibrinogen and blood fibrinogen he believes can happen directly without any of the preliminary reactions of the classic theory, and the production of small amounts of fibrin in that way sets off the classic mechanism.

The classic theory as I presented it in the first slide seems to be the one com monly accepted in this country, and is as good as any for the interpretation of clinical phenomena

I suppose most of you have seen articles by Kugelmass regarding his idea of measuring increased or decreased congulability of the blood by means of a "clot ting index " He seems to have been a pupil of Bordet's, and has done a good deal of work in New York on this question of measuring coagulability, both as a diagnostic procedure and as a preoperative precaution He derives what he calls a clotting index by taking the product of the factors which favor clot forms tion and dividing by the anticongulant factor, antithrombin (Slide) mal prothrombin index is given an arbitrary value of one. The fibrinogen index is five tenths, because that is not an arbitrary value. It represents the ratio of the refractive power of the serum to that of the plasma, which is normally one The prothrombin index is the relation of the prothrombin time in a particu lar blood to that of a normal control All theories agree in assigning to the platelets the most important place in initiating the clotting process measures the platelet value by taking 200,000 as the normal count, and 50 per cent as normal disintegration in one hour, thus getting a normal figure of 100,000 for active platelets, to which he assigns a value of one in his index thrombin, again, is given a normal index of one I shall not go into the methods of determining these values, which are to be found in laboratory manuals values assigned give a normal index of five tenths, from which Kugelmass allows a variation of two tenths as within normal range

This scheme is, I think, rather a good one—not so important in the diagnosis of the marked disorders as in minor things, such as the tendency to oozing after a tonsil operation, tooth extraction, or something of that kind. Here is a sample of how it works out. (Slide.) This was a hemophilic patient. The prothrombin index was 0.44, fibrinogen, 0.5, platelet lysis 10 per cent. (index. 0.2), antithrombin index 1.2. The clotting index is 0.036. The clotting time of the patient's blood was thirty minutes. Kugelmass emphasizes the very great lowering of the clotting index in hemophilia as compared with almost any other condition. It is evident, however, that in thrombocytopenic purpura with a very low plate let count the index will be fully as low.

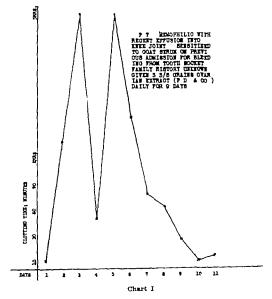
With this rather sketchy background of the clotting mechanism, I wish to say some things about hemophilia Dr Sanford is to talk of some of the other disorders

You all know that hemophilia is the great example of hereditary disease. It is also an example of sex linked heredity, never transmitted direct by the male, but through the daughters of the male to their male offspring. Or, it may go through two or more female generations and finally appear in male descendants

(Slide) Here is a rather simple family tree of a hemophilic family, in which you may see how these things go For instance, you will see in one of the lines of female descent how the trait has gone through two female generations to be come manifest finally in their male descendants. This does not show some of the things that Dr Birch speaks of, and that I have not seen mentioned elsewhere

ourselves of any real effect. It is an easy treatment to carry out, and deserves consideration as one of the possibilities for the routine handling of the hemophilic, as this is a condition in which one wishes to do everything possible.

Another treatment which has been in the limelight lately is that of the use of ovarian extract. This is not new It was based originally on the peculiar sex limited heredity of the durease, and the not unnatural assumption that the sex hormone might have something to do with the immunity of the female. The new thing is the observation by Dr Carrol Birch that the small amount of the female hormone said to be present normally in the male urine is absent from the urine of the hemophilic. She and some others have reported remarkable results from intramuscular injection of the hormone as a therapeutic agent, and I suspect that everyone who has hemophilics in his care has given it a trial or considered doing so

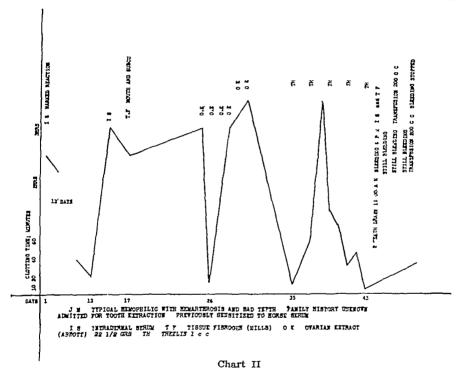


We have been trying it on some of our homophilics recently I do not think that our results are at all conclusive because we have not enough of them, but I should like to show you what we have done.

Chart I shows the curve of daily determinations of clotting time in one of our patients who came in just after an efficient into one of the knee joints. Bleeding had stopped when he came in and we kept him to make sure that it was not go ing to recur utilizing the hospital stay to observe the effect of daily injections of ovarian extract on the clotting time. The dose here was one ampule containing three and three-fifths grains of a preparation of the whole ovary made by Parke Davis & Co. The chart shows very nicely the wide fluctuations in the clotting

time of which I have spoken—from ten minutes to five hours in this case. The chart for the first seven days looks like a malaria fever chart. From the seventh to the eleventh day you will notice that there was a gradual drop in the clotting time from ninety minutes to fifteen minutes, without the wide fluctuations. One might conclude that daily administration of ovarian extract for eleven days finally brought about a lessening of the clotting time. Perhaps it did. It did not, however, have prompt enough effect to have helped if the boy had been brought in bleeding.

Chart II is the clotting time chart from a case in which we used all methods to prepare for tooth extraction a boy who had a number of bad teeth and was having troublesome bleeding from the gums. He had also an old hemarthrosis and had previously been sensitized to goat serum. The chart shows the same wide



range in clotting time seen in the first one, but with a tendency to remain high for longer periods After a period of preliminary observation during which the effects of intradermal serum and "tissue fibrogen" (a preparation advocated by Mills) were tried, with negligible results, ovarian extract was administered, first a preparation of the whole gland in twenty six grain doses, then Parke, The curve during this period resembles that Davis' Theelin, one ampule daily in the first chart, in that after about fourteen days of the gland treatment the excursions became less wide and the time seemed to be steadily diminishing the seventeenth day it had come down to ten minutes, and we thought this a favor able time for the tooth extraction Two teeth were drawn in the morning of this Intradermal serum was adminis By evening there was free hemorrhage tered, and tissue fibrogen, by mouth and subcutaneously, both without effect hemorrhage stopped finally after two transfusions You will notice that clotting time determinations were not always made daily in this case. This was because

of a difficulty which we have encountered in other hemophilics, and for which I have no definite explanation. We use venous blood for these determinations. At times there is such a marked tendency to thrombesis at the point of puncture that we cannot use the vein. I think that this may be a mechanical effect of platelet agglutination at this point without disinterration.

I have not charted one case, treated before we began to try the everian extract. This was another in which we wished to extract teeth and it was our first trial of the protein sensitization method. We sensitized the patient drew two teeth and produced a sharp reaction with intradormal serum. The child bled very badly, and needed three large transfusions to save him.

Our results with these newer treatments do not seem to have brought out much in their favor I do not feel, however that we have gone far enough with them to draw definite conclusions and I am inclined to try them further It may be that we have not used large enough doses of ovarian extract. I believe that Birch has given as much as eighty grains gauging her desage by the clotting time. After our experiences with the wide variations in this measurement I do not see how the dose can be satisfactorily gauged by it. We got no effect at all from single doses and daily doses of eighty grains would be a pretty expensive method.

The present status of the therapy of hemophilia would seem to be that we have two methods for which there is enough favorable testimony so that they deserve further careful trial. We cannot, however depend on them to prevent or to check severe bleeding and are not safe in undertaking any surgical precedure on a hemophilic without being prepared to apply the only measure which has been proved to be reliable—transfusion. I think that we have sometimes made the mistake in transfusing for hemophilic hemorrhage of giving too small transfusions or of not giving them early enough. In both hemophilis and pur pura I believe that large transfusions are better than small ones and I am sure that they are more effective if they are given early, without waiting to see how bad the bleeding is roung to be.

We will pause here for discussion before listening to Dr Sanford

DR. H. B HAMILTON (OMAIA NEBRASKA) -My understanding is that Dr Mills injects the serum near the bleeding point, is that correct?

DR COOLEY—1es but it depends upon where the bleeding point is and can not always be done. It is possible only in the minor superficial injuries such as bleeding from scratches, etc. As a matter of fact, we have had very little occasion to treat those things.

Another thing about hemophilia is that very commonly we have bleeding from some one of the nuccus membranes—the fronum of the tongue, the gums or some similiar place where intradermal injections are not practicable. The same difficulty is met with in nessbleed

DR. MARTIN D OTT (DAVENFORT IOWA) -Oan you make local applications for noseblood?

DB. COOLEY—I do not believe it would be possible. A thing we have tried with bleeding gums is to pack them with tissue fibrogen. We have never had any effect from it. One would think that putting a substance which really contains a good deal of cophalin right into the bleeding cavity might help but we have never been able to see that it did We have had no luck with tissue fibrogen given either by mouth, by local injection or direct local application

DR STERLING H ASHMUN (DATTON, OHIO) -I have been very much in torested in this work of the Cincinnati group, having heard them discuss their

claims A discussion came up in a meeting, as to the best method of sensitizing a child. For instance, a young baby might be sensitized to tuberculin. Since most people are sensitized to tuberculin early in life, it might be a good thing to use intradermally as the substance to which the child might be sensitive. That might be tried early in life. They also found the use of ovarian extract to be a help. We should have thought of this a long time ago since the female does not have hemophilia and the ovarian substance is the one thing she probably has that the male does not. Certain workers believe that females sometimes do have what they consider to be hemophilia.

If there has been more than one ancestor with hemophilia, the female offspring are all the more hable to have hemophilia We should advise that hemophilics should not marry At the Central States Pediatric Society meeting last year, the use of muscle tissue from the individual to stop the hemorrhage was reported That would be a good source for tissue fibrogen in any individual when an opera tion was contemplated If a piece of the tissue could be planted or fastened right into the wound it might help, even placing it in a tooth socket might help to control the hemorrhage Since ovarian extract is involved, might not those cases in which the female shows a tendency to hemophilia or purpura show some involvement of the pituitary? Dr Cooley mentioned the finding of poor teeth so constantly in hemophilics. That suggests also a deficiency in calcium metabo hism as well as a capillary penetrability. We have had favorable results in preventing, or in lessening the frequency of ordinary hemorrhage in circumcision by the use of a high protein diet in the first few days of life. I am thoroughly con vinced that the high protein diet does aid even in hemophilics, in lessening the minutes, we found after circumcision no clotting whatever, until after the in jection of fibrogen, then in five minutes there was good clotting and the patient made a good recovery

DR T COOK SMITH (Louisville, Ky) —Of what does the proof of diagnosis in the very young consist?

DR COOLEY—I think in the very young infant the diagnosis is bound to be a little doubtful. On the whole, two things are probably more important than any of the others. First, the great prolongation of venous clotting time. This however, has to be measured more than once, because you might run into one of these periods where the clotting time is pretty short, like some of those I showed on the charts. Therefore, you would have to make more than one test to insure accuracy, although if the child is actually bleeding, the chances are that you will find the clotting time prolonged. Second, failure of platelet disintegration is equilly important in the hematologic diagnosis and the prolonged antithrombin time, which apparently goes with the delay in platelet disintegration. While it is a somewhat difficult thing to measure, I really think failure of plate let disintegration is perhaps the best test we have of definite hemophilia. A very low clotting index is very strongly suggestive.

DR SMITH-Is there any experience in your chinic to show that there are female hemophilies?

DR COOLEY—We have no experience indicating that there are There are some reported observations of disturbances in the clotting mechanism in females of hemophilic families but I am not aware of any evidence of true hemophilia Dr Gorter, what do you do with hemophilia in your clinic?

DR E GORTER (LEIDEN, HOLLAND) —We have had almost the same experience you have had in regard to hemophilia We have also tried ovarian extract in the

hope it would be useful but we could not find any definite results. I have been asked, and I would like to ask von whether a different form of preparation of the ovarian extract might account for difference in results? I feel as you do that it is very important to make large transfusions and to do so early. If you apply transfusion from the very beginning of bleeding I think results are temporary I think they hast almost one week and then it is necessary to repeat it

May I ask another question with regard to the disintegration of platelets! You will find in the literature a description of thrombasthenia by Glanzmann, which indicates that failure of platelet disintegration may occur in other conditions than hemophilm. Do you believe in the existence of this thrombasthenia as a cause of purpuric conditions! Would this somewhat complicate the value of the prothrombin test or the disintegration of platelets in the diagnosis of hemophilia!

DB COOLEY —I have no knowledge of that disease except from Glanzmann s description, so I am afraid I could not answer I think it must be very rare. As to transfusion, I would not have you think I am not optimistic about transfusion I think it is the best treatment we have We use it freely and we have never lost a patient from himophilis

As to the preparations of ovarian extract, Dr Birch has used a good many of these. As you noticed, we used three different ones. I do not remember that she has had definitely more favorable results from one than from another. She simply stated, as I remember that she tried a number of preparations and she tried also some very large dozes and seemed to think the dozes should vary in accordance with the clotting time.

From the clotting times I charted, I do not see how you could use them as a basis for your doses as when you see a child with a clotting time one day of ten minutes and the next day of five hours, your choice is cortainly loubtful. We apparently got as good results from the preparation of which we gave somewhat less than four grains at a dose, as we did from the other preparation of which we gave twenty six grains or from the supposedly pure Theelin.

DR. GORTER —Is there any confirmation by animal experimentation of the reported testicular atrophy after ovarian extract administration?

DR COOLEY -I have not been able to learn of any I have inquired of men working with ovarian extract in animals but have not heard of any definite observations on this subject

Do any of you want to go into the question of the clotting mechanism itself?

I have a feeling that a discussion on theories of clotting does not get us very far I mean to say that the observed facts are pretty generally recognized, and that beyond that we get into a region of theory which cannot be valuable clint cally I feel the clinican may just as well rest where he is for the time being Now things are coming up all the time

The relation of earbohydrate metabolism to electing is one of the things which seem to be getting quite a bit of discussion in some of the foreign clinics and out of which I have not been able to get much so far

DR. GORTER —Is it not possible that there is not only failure of platelet dis integration but some more general disturbance of reticuloendothelial function?

DR. COOLEY—We have by no means reached a complete understanding of the bleeding disorders. I think that all of us who have busied ourselves with the blood have come in recent years to feel that eventually we may find that several of the disorders which we do not understand very well are really dependent on dysfunction of the reticuloendothelium.

One of the things about the clotting mechanism which no theory explains satis factorily is the failure of clot retraction with a scarcity of platelets. Mills, who looks on clotting as a reversible reaction, and believes that fibrin disintegrates with liberation of thrombin, thinks that the explanation may lie in this (I do not quite understand his reasoning). Howell says that the only suggestion he has is that it may be a matter of a quantitative lack of fibrin in the clot

If there is no further discussion, I will ask Dr Sanford to go on with the purpuras

#### Purpuras

DR HEYWORTH SANFORD (CHICAGO) —In the very loose classification of conditions we speak of as purpuras it seems obvious that we are dealing with a number of etiological factors, which it should not be difficult to separate. In one recent article, however, all the purpuras are thrown into one large group, without recognition of the platelets as an etiological factor, so that it is evident there is still a good deal of confusion

It seems to me the best method of classification is to divide them into two groups first, the thrombocytopenic type, in which the platelets are distinctly diminished, and second, the nonthrombocytopenic type, in which there is no change in the clotting factors

In the first group, that in which the platelets are diminished, we have a pr mary, "idiopathic" type, in which there is no change in any of the constituents of the blood except the platelets, and various secondary forms, in which the blood shows changes due to the primary disorder. The platelets are always markedly reduced, and the bleeding time as a rule is lengthened, usually to more than seven minutes. How low must the platelet count be to cause danger of bleeding? Most writers agree that when the count falls below 100,000, purpura may develop McLean published in 1921 a study of twenty one cases, all of which the count was below 100,000, the lowest being 10,000

The secondary thrombocytopenias may be subdivided again into a group in which the platelet deficiency is due to interference with marrow productivity by tumors, leucemic infiltrations, aplastic anemia, etc., and another in which in fection plays the chief etiologic rôle. Certain acute infections, diphtheria, scar let fever, influenza, and notably the streptococcus infections, are particularly prone to lower the platelets. Streptococcus foci which remain for any time all most invariably cause a marked reduction. Among the chronic infections, tuber culosis and syphilis are likely to have this effect. In this group, we are evidently dealing with conditions in which treatment must be directed to the underlying cause.

The most interesting member of the thrombocytopenic group is the so called essential thrombocytopenic purpura, or Werlhof's disease, one of the first blood disorders to be studied. Werlhof published his description in 1735. The chief characteristics are purpura, possibly some fever, increased bleeding time and decrease in platelets. The important thing is the decrease in platelets, the primary cause of the condition. When clot formation in this type of purpura is studied with the ultramicroscope the fibrin threads are seen to be deposited, and clotting seems to proceed in the normal way, but the clot which is formed is peculiarly soft and dose not contract with separation of the serum. Consequently, bleeding continues for a longer time

Washed platelets from a patient with essential thrombocytopenic purpura mixed with serum from a normal person from which the platelets have been removed will cause that serum to clot, while washed platelets from a normal per son will cause normal clotting of the blood of the purpuric patient. These facts

are proof that the difficulty does not be either in any defect in the patient a platelets or in anything in the plasma but wholly in the shortage of platelets.

Deficiency of platelets must be due to one of two reasons—either the production in the marrow is inndequate or they are destroyed somewhere in the circulation. In the secondary thromber-ytopenias defective production is probably to blame—Against this as the cause of essential thromber-ytopenia is the fact that in autopsies on patients dying from this disease we do not find evidence of disturbance or destruction of plastocytes in the marrow—Furthermore in secondary thrombec-ytopenia due to aplasts or displacement of marrow by tumors the pur pura is never so severe as in the idequatible form

The other explanation is that of destruction somewhere in the circulation. The reticuloundothelial system, a conception for which we are indebted to Aschoff, is composed of peculiar cells found in splein liver lymph nodes and other similar dissue, the spleen containing the greater proportion of them. The large monon nuclear phagoestes which are known to destroy platelets are a product of this system. If trypan blue is injected into an animal these cells take it up and be come "blocked." This is followed by an increase in the platelets. Cole in 1907 developed an antiplatelet serum. If this sorum is injected into an animal there is an immediate decrease in platelets unless the spleen has first been removed in which case there is no decrease.

We are justified, therefore, in concluding that in essential thromboevtopenic purpura the platelet deficiency is due not to defective formation but to destruction by the reticuloendothelium in which the apleen has the chief part

This type of purpura has a scasonal tendency. It is seen more often in the spring. Again it is somewhat more common in females, and is likely to manifest itself before the third decade of life. The fact that it is a disease characterized by spontaneous remissions probably accounts for the great variety of treatment to be found recommended in the literature.

The idea of dietary treatment is old. Willan in 1801 advised fresh air and abundant diet. Kugolmass recommends a high protein regime. Almost all of the vitamins have had their advocates. Phillips in 1931 reported platelet increase following viostorol. Cramer and Drew in 1923 reported platelet increase and Sooy and Moise in 1920 platelet increase and remission of symptoms following ultraviolet irradiation. This has not been confirmed by later observers. Jones and Tocantina, reporting a sories of cases in 1933, mention two cases they were unable to control by transfusion in which the platelet count was increased by plinitary extract. Three interesting carefully studied cases have been reported in which cure seems to have followed the administration of bothrops anti-enom. As the patients were soldiers serving in the Canal Zone, there may have been some unrecognized factor though the symptoms were typical of essential thrombotytopenia.

There is general agreement as to the advisability of clearing up feel of in fection. Secondary purpurus are often caused by such feel and recurrences of essential thrombocytopenia are likely to be initiated by flare-ups of infection.

Transfusion is almost universally considered the method of choice for control of the immediate attack. I was interested in Dr. Cooley's remarks about the desirability of large transfusions, because Jones and Tocantins advocate frequent small ones. They say they have had just as good results from 25 to 200 c.e. of blood injected at frequent intervals as from 500 to 1,000 c.e. at longer intervals. They any also it must be given intravenously, which is not in agreement with our experience. We think we have had as good results with intraportionen in jections as with intravenous administration.

Finally, we come to the question of surgical intervention by removal of the spleen. While this seems logical, and most writers report favorable results, the statistics are not so good as we should like them to be. I think that Whipple's figures published in 1926 are the best. He reported results of splenectomy in eighty one cases, most of which he had been able to follow for five or six years. Of the eighty one patients, 50 per cent were definitely improved after operation, and of that 50 per cent, 60 per cent were permanently benefited.

There are indications for and against splenectomy. Most observers think that if it is possible to control the condition by other means, such as transfusion, this is advisable, though it is not wise, of course, to wait too long. McLean thinks that splenectomy should be performed in two types of cases, first, in those in which the bleeding is so free that the patient will evidently soon be moribund, and second, in the chronic case with frequent relapses and resultant secondary anemia which is interfering with the patient's development

Payr, in 1931, reported thirty four cases in which the splenic artery had been ligated. The results, though slower, were apparently very good, and the operation is less dangerous because the shock is less. There have been no reports of thrombosis of the artery. This may prove to be the treatment of choice in selected cases.

The prognosis in this type of purpura varies greatly. The patients seem to have relapses alternating with periods of comparatively good health. McLean had four deaths in his series of twenty five, and Jones and Tocantin nine in fifty three cases.

So much for the thrombocytopenic purpuras

In the second large group we have the cases in which there is neither platelet lack nor any other derangement of the clotting mechanism. Certain of these have a definite etiology. Malnutrition, lack of vitamin C and other similar conditions may cause purpura. Some infections, particularly respiratory, not uncommonly have this effect, as do mechanical factors such as varieose veins, certain tumors and pertussis.

Most of the cases of nonthrombocytopenic purpura have no such definite etiology. By far the largest number of all the purpuras fall into this class, and they seem to represent different grades of the same condition. We are all fa miliar with the so called purpura simplex, of which we see a good deal, and which has no symptoms except purpuric spots—large black and blue spots on the extremities, or showers of smaller spots all over the body. There may be a little falling off of appetite, usually some nervous disturbance, but that is about all. The condition lasts from two days to two weeks and then clears up. There are almost always associated allergic symptoms such as urticaria or other manifestations of the allergic constitution. Going a little further, we have the "arthritic" type, with effusion of blood into the joints and pain apparently out of proportion to the swelling. This form, though more severe, runs the same course. Then we have the abdominal type known as "Henoch's purpura," in which, in addition to purpuric spots and joint symptoms there is abdominal pain, diarrhea and vomiting and bleeding from the gastrointestinal mucosa

Though there is no universal agreement, these forms of purpura are quite generally believed to be allergic phenomena. It is usually said there is no change in the blood elements. This is certainly true so far as the platelets are concerned. We have recently had a case of Henoch's purpura in which, in testing the clotting factors in the way Dr. Cooley has described, we found the fibrinogen decreased to less than half normal value. Lack of fibrinogen in the blood is usually evidence of some disturbance of liver function. The lack can, of course, be congenital, and it may occur in allergic states. The blood fibrinogen is almost allergic states.

ways found diminished in experimental allergy. I was not aware this observation had been made in purpura before but I find that Bruhl in Germany reported two cases in 1931 in which there was the same finding

The treatment of this kind of purpura i. of course purely problematical Whatever you do for it might be called simply a stab in the dark. The customary thing is to put the child on a simple nutritious diet, giving plenty of orange juice and all other vitamins and a high proportion of protein, and assumpt that recovery will soon follow. I think there is a basis for that assumption for if those purpuras are simply allergic manifestations, and there is a lack of fibringen in the more severe forms, that lack at least may be compensated for by the in creased protein.

DR COOLEY -- I would like to add a few words, particularly about thrombocytopenic purpura, from our own experience. In the first place, as to splenectomy
and when you are going to do it.

The first attack of purpura is the critical attack. It seems to be true, un doubtedly that acute infections may bring on a temporary thrombocytopenic state. When you see a child in his first attack of purpura you always have to realize he may never have another. You do not want to think of extreme thera pecutic measures at that time because it may be not only his first, but his last at tack.

So it has come to be a rule with us that we will not consider splenectomy in the first attack, unless we are absolutely driven to it. It may not be a chronic condition at all.

Then there is always the question, if the thing does prove to be chronic, or recurrent how important it is to the individual patient—and that is a matter of observation. Performing spienectomy only in emergency cases our luck has been very good. I think, with one exception every case on which we have performed spienectomy so far, has been cured but we have been pretty caraful in how we select them. The one case we have not cured was one which we lost just a week or so ago, and it is a good illustration of the complete fatility of treatment in some types of thrombocytopenic purpura.

This child came in after a first attack following a glandular infection preceded by measles. She came in bleeding from the mouth and one car. In the course of her stay in the hospital she developed bleeding from the intestines and kidney Bleeding from the mouth and car stopped after several transfusions. We were unable to stop the bleeding from kidney and intestine and we tried overything with one exception (and that is the antivenom) that has been recommended on any apparently logical basis for the treatment of purpurs

The child was less than a year old. She had ten transfusions, about 1700 cc. of blood

We finally made up our minds entirely against what would ordinarily be our best judgment, to take the child's spleen out. And we did. It proved to be a very difficult splenectomy By the way this is a good time to say that splenectomy is not a thing to be undertaken lightly because it is often a very serious operation.

This child's spicen, perhaps 50 per cont larger than normal, was protty well tucked up under the ribs and difficult to get out. The child died of postopera tive shock. If she had survived the operation I do not know whether we should have put a stop to the purpura or not. That is the first splenectomy for purpura we have lost.

We have had a number of patients whom we sent home with instructions that they were to be brought back immediately if they had another attack and at least 50 per cent have never returned. We have had another percentage

that came back with rather minor bleeding so we have felt justified in not doing splenectomy. There has been a rather small number whose spleens we have removed with perfectly good results. We always feel we may get a return of symptoms for one perfectly definite reason, that is, it is perfectly possible that a supernumerary spleen may be overlooked in doing a splenectomy. We all know how rapidly they develop after the principal organ has been removed. I believe if I saw a patient with a recurrence, I should ask the surgeon to reopen the abdomen to make sure there had not been a development of a secondary spleen. We have never had occasion to do that, still I believe it would be a logical thing to do

We have seen two cases in whom bleeding was not readily stopped by transfusion in which it was stopped by one of the biologic anticongulants, the one we use most often and which is called "thromboplastin." We have had two cases of obstinate nosebleed in thrombo cytopenia stopped by that method when transfusion failed. This is quite against what you will ordinarily see in the literature but it is not a common occurrence

In the allergic type we have also just had our first death. The condition was interesting because I have not seen it reported. This child came in with the ordinary picture of Henock's purpura, i.e., the peculiar type of abdominal pain, followed a few days later by purpuric skin manifestations, which went through the ordinary course. The child had practically recovered although he still had a few spots on the skin, so we thought we were justified in allowing him to go home. He apparently completely recovered at home but suddenly he developed convulsions and died. The autopsy revealed multiple petechial hemorrhages scat tered throughout the brain. That is the first thing of that kind I have seen

One more thing about the treatment of the allergic type of purpura. While we have never found anything definite, we have felt we got better results from the administration of calcium than from anything else we have done

DR J A. BIGLER (CHICAGO) —Is there any relation between the decrease of platelets and the amount of types of hemorrhage you may find?

### DR SANFORD-No

DR BIGLER—The reason I asked is because in certain conditions you may have a marked reduction of platelets, down even to 10,000 and still have no evidence of purpura hemorrhagica. Thrombocytopenic purpura is due to reduction of platelets. Why do not all patients with few platelets bleed?

DR SANFORD—So far as I know, there is no answer. It is just one of those things one cannot explain. Of course, the idea that the condition is due entirely to platelet decrease in not acceptable to everyone. McLean was under the impression there were other factors.

DR BIGLER—It is certainly true that with a marked reduction of platelets, trauma has very little to do with hemorrhages. I do not believe anyone has an explanation for some of the peculiar things one observes. It is true, as you say, that there are patients who have almost no platelets at all and that some of these will go for long periods without any bleeding. There seems to be a good deal of evidence that there must be something aside from the lack of platelets which is related to the purpuric manifestions. There must be something which favors passage of the blood through the vessel walls aside from lack of platelets. The evidence for hypersplenism or hyperactivity of the reticuloendothelial system in thrombocytopenia, I think is pretty good. Here again we think it is possible that the disease is actually a disease of the whole system rather than simply of the spleen, although the spleen, being the main part of the reticuloendothelial

system, is probably the main factor in the production of purpura by the destruction of the platelets. On the other hand, it is possible that under some conditions the rest of the reticuloendothelial system is more active in proportion to the spleen than usual and that might explain the failure of splenectomy in some of the cases where it has been reporte i—that in those cases, the rest of the reticuloendothelial system tissue was more active proportionately

All we know definitely is that the condition is obviously connected largely with platelet deficiency and removal of the spicen cures or helps to cure this deficiency Therefore, we have to lay most of the disease process to the spicen. As to the rest of the process, I think we are still in the dark.

DR SMITH—lou said you thought a good many of these cases of purpura simplex were allergic. Have you any it a what food does it! Do you think it is bacterial?

DR SANFORD -It might be

DR COOLF1 -I have known f ju t one case that gave definite reactions to food.

DR. SMITH.—We had a little girl who had a rash, and ecchymosis of the skin. A physician had removed a large mass from her neck at one time. The attacks kept recurring and for lack of something better to do I put her on a milk duct and she became much worse. I then removed all milk and she cleared up completely. I put her back on milk and she became worse, but her skin did not react to the milk test.

DR ASHMUN—It has been reported in the literature that the platelet count taken after a meal is raised, sometimes a hundred thousand or more so we should avoid taking platelet counts soon after digestion of food. What is your idea relative to the modus ope and of that? Is it due to the fact that the blood is being used in digestion and there is less going to the spleen? What is the process? If we were to treat these patients by diet would it be necessary to use any particular type of protein or just more protein than usual?

DR SANFORD—Rugelmass from his experiments thought any type of protein had more effect on the platelet formation than other types of food. Whipple found that liver was very efficient in promoting blood regeneration and Mackay in several cases of pernicious anemin, was able to increase the platelets to quite high figures, that is above 400,000 by feeding liver to the patients. This would indicate that the platelet forming tissues participate in the general improvement in homopoletic activity produced by liver or rather a liver diet

DR. BIGLER -What method of platelet count do you use?

DR SANFORD-I think the sodium citrate method is as easy as any You can do it quicker than any other way

DR BIGLER .- Is there any such thing as a hyperplatemia?

DR SANFORD-I do not know

DB COOLEY.—There are people who believe there is, that the platelet in crosse after splenectomy may reach a dangerous point I have seen some very high platelet counts but I have not seen any unpleasant results from them. There are people who believe they can happen and that there may be a tendency to thrombosis. Of course, a certain number of platelets normally go to pieces in the circulation. They seem to believe, and probably logically that in proportion a greater number will go to pieces when the count is high and there may be

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told her it was probably an angioneurous edoma. A few hours later she brought the child to the office and he was perfectly normal. It recurred on the baby's check and lip

Three days later the child was afebrile and had no temperature. The child later developed temperature 108. A trenahn was given. I have seen no definite reports of angioneurotic edema in the medulla or thermo-regulating center. I do not know how one could prove this happened but as quickly as we administered adrenahn the temperature went of which eight or nine degrees.

Again, after two or three days the child suddenly developed distress in the stomach and the entire upper half of the abdomen became greatly enlarged. The child was in great distress and later about a quart of a chocolate-like material was siphoned off from the stomach which reacted very strongly to blood. This recurred again two days later and on the second occasion the child had some fover. Following this we tested the child for many things from the allergic standpoint except house dust. Results of these tests were negative.

DR OTT—I have not had a case of purpura under my care but certain other conditions like some of the upper respiratory infections have brought out certain points in relation to allorgy. In one case of a child I could not get a sample of the respiratory secretion but I took cultures from the stool. I found that the child gave a very good epidermal reaction to these organisms. I then desensitized the patient. The patient had surprisingly good results in a few days. One case is not enough to prove anything but I think it might be a good thing to look at allorgy from a bacterial standpoint rather than entirely from a food stand point.

DR SANFORD—Of course all this subject of purpuras is not clear What I have given you is simply the usual ideas of the present time As Dr Gorter said it does not work out nearly so nicely as we like to think that those are all allergic manifestations. There have been a few cases in which work has been done to indicate that it might be that type but on the whole there are just as many cases where it is absolutely impossible to find any reason. I think your suggestion about the betteriological viewpoint is certainly worth while

QUESTION -Dr Gorter in the first case you cited of what did the child die!

DR GORTER -It was one of a large group of children. We did not have many autopaics. One might say it is almost a description of leucemia

DR COOLEY—I have seen several such cases. Some of the writers make quite a point of the fact that one can see all grades between thrombocytopenic purpurs and an outspoken aplastic anomia. There is a considerable group in which apparently there is a marrow hypoplassa. I wonder whother that would not apply to the group you are speaking of

DR GORTER.—Yes, I should think so I think that in most cases of real aplastic anemia it starts so to speak, with acute symptoms and death occurs in six weeks or so with high fever

DR COOLEY—I think there is a very definite difference between what I speak of as hypoplastic anemia and aplastic anemia. I think sometimes the platelets are more involved than the other blood elements in the hypoplastic state. The pathologic pictures are very different in the bone marrow in the two conditions.

DR SANFORD -In answer to a question about ultraviolet therapy the results are variable sometimes there is an increase. Certainly in the newborn

there will be a slight increase in platelets following ultraviolet radiation but the newborn is most unstable and there is no reason to expect that the adult would react similarly

DR COOLEY—It seems to me the argument for that type of treatment is not very good because in experimental animals we are not dealing with a condition of excessive platelet destruction. The difficulty in thrombocytopenic pur pura is that you would not expect to be cured by any temporary or minor increase in platelet production because they are all destroyed. That seems to be true except in some secondary forms of purpura. For instance, where the marrow is crowded out by leucemic infiltration. If the productivity of what marrow is left could be increased, that might help

Dr Sanford, were you going to say anything about the hemorrhagic disease of the newborn?

# Hemorrhagic Disease of the Newborn

DR H N SANFORD—Occasionally, in the newborn somewhere between the second and eighth days of life, we meet with a type of hemorrhage for which there is no clear explanation. The forms for which there is a definite etiology, such as in fection, septicemia, trauma and congenital syphilis, have been excluded. Clinically there is nothing particularly characteristic except the bleeding. This may be from the mucous membrane of the nose or gastrointestinal tract, the cord, or the meninges. There are no other symptoms except the secondary anemia. The bleeding rarely comes before the third day, and rarely after the sixth. To judge from reports in the literature, the frequency of this condition must be decreasing rapidly. Le Queux's statistics, the earliest I know, showed an incidence of nearly 35 per cent. The last series of any note is one from Grob in Lucerne, in which he found only fifty cases in ten years.

As to the cause of the condition, every one of the clotting factors mentioned by Dr Cooley has been reported as being affected. Whipple found a decrease in prothrombin, Schloss and Kommisky found lack of thrombin in one case, and of fibrinogen in another, Kugelmass found decreased fibrinogen. All are agreed that the platelets are not diminished. Grob found no lack of them in any of his cases

This hemorrhagic state of the newborn must be distinguished from bleeding due to mechanical factors Bonar found chemical evidence of blood in 30 An infant may vomit per cent of stools from one hundred nine newborn babies swallowed blood if the mother's nipples are cracked Hemorrhagic disease is excluded by the absence of any change in bleeding or clotting time his studies of normal bleeding and clotting time in the newborn (made with capillary blood) found that at birth the infant has times comparable with those of the adult (five or six minutes' clotting and three or four minutes' bleeding time), and that the time tends to increase to a maximum about the fourth day, after which they drop to normal If this is tiue, practically every newborn child is in a prehemorrhagic state Several years ago we determined the clotting factors in a group of thirty five newborn We found thrombin and antithrombin a little lower than normal and fibrinogen slightly higher. If this is the rule, there must be other factors at work in the hemorrhagic state We endeavored to find things which would alter the proportions of the clotting elements terol and ultraviolet light had no effect. The first change observed followed withholding protein and fat from the food This was done by keeping the child from the breast for five days, giving ample salts and carbohydrates procedure we obtained a distinct lessening of fibrinogen, but hardly enough to cause bleeding

The decrease in this condition seems very striking to me Since we have been interested in the study of the clotting factors in the last five years we have not had a single case of hemorrhagic disease in which we could make those determina tions. We have had two or three brought in from outside but in too advanced a stage.

As to prophylactic treatment, that, of course is an obstetric problem, and I believe the lessened incidence of the disease is due to the fact that most of the mothers' diets are better. We never see it in private practice and most mothers in dispensary groups have a well supervised diet. Moore was able to produce a hemorrhagic condition experimentally by feeding the mother a diet lacking in vitamin B. Graham, in 1910 found that young animals subjected to prolonged anosthesia showed increase in bleeding and clotting time. The same thing has been shown in the child born after a long ether or ethylene anesthesia. As to obstetric manipulations, I have never observed that they had anything to do with producing hemorrhagic disease. Most of the cases have followed normal deliveries. Kugelmass advocates giving gelatin from birth for prophylaxia. Most babies will take gelatin readily, but it seems to me that if one wishes to administer protein, it might as well be in the form of a high protein food that the child can utilize

In treatment of the actual hemorrhage I think that anything except blood is useless calcium, viosterol thromboplastin etc., are simply a waste of time. For the past fifteen years immediate injection of whole blood has been recognized as the only effective treatment. Dr Smith asked about mother s blood in the hemophilic. There is a feeling among obstetricians that they have better results in the hemorrhagic disease from the use of the father's blood instead of the mother a. In the past few years we have tried to determine whether father s blood mother's blood or 'foreign' blood has the most effect on the clotting factors. From our figures it would appear that we had somewhat more effect from the foreign blood. Father's blood comes next and the mother's blood gives somewhat the poorest results. In using foreign blood one must of course be sure about the Wassermann test, while one does not have to worry about that so far as the parents blood is concerned. If there is anything to an inherited or maternal tendency in the disease it might be carried over in the mother a blood. I like to use the father s blood when I can We have had very good results from giving small quantities (10 c.c.) of father a blood intramuscularly In severe cases we have given 50 to 100 c.c intraperitoneally and thought we got as good results as from intravenous injection. We never give large amounts that is necessary only in rare cases. Usually the bleeding can be controlled satisfactorily by small intramuscular injections.

DR. COOLEY—The idea of starting with the small amounts of blood how ever is a little dangerous but, of course, that has been extensively advocated Nearly fifteen or twenty years ago it was a general procedure and I saw several cases that made me reach the conclusion I would rather play safe and give more

QUESTION -- Wouldn t it be better to give a transfusion and begin life less anemie!

DB SANFORD—My feeling is that some of these patients are very anomic Such a child should have the blood replaced in a very short period of time. It certainly does not do any harm and I think there is everything in favor of it.

QUESTION -What voins do you usually use in the newborn!

DR COOLEY.—If you are particularly expert in manipulation, it is surprising what you can do in some of the smaller veins. I know one man who gives trans

fusions in the newborn infant in the veins of the scalp but that takes practice We use the saphenous vein more than any other

DR ASHMUN—Perhaps you are familiar with Dr Wagner's series in Cincinnati He had 200 cases of premature infants he reported in which he used the blood as prevention of hemorrhagic disease. He has another 100 cases now making a total of 300 cases. He gives them either the mother's or the father's blood and has not had a hemorrhagic disease develop in any one of those 300

DR COOLEY—Dr Dunham tells me they have studied a series of 1,000 new born infants and in that series, where nothing was done for prophylaxis, there were only 3 cases of hemorrhagic disease. She very properly said, it would take a fairly large series of cases to prove results from prophylactic treatment of any kind. In other words, in the series of 300 you cite, you would not have expected more than one case of hemorrhagic disease.

DR ASHMUN —In view of the fact that there is such a small incidence, is it not likely that diet plays a large part?

DR COOLEY—Dr Dunham was asking what I thought they might do to study that question further She suggested the thing to do was to study the mothers

DR SMITH —The premature infants would be better to receive the father's blood, according to your findings, Dr Sanford.

DR SANFORD—I do not remember seeing a case of hemorrhagic disease in the premature infant. In fact, we have not had a case on our newborn service of hemorrhagic disease in the last five years. The only cases we have seen are those coming in from the outside

DR ASHMUN—Do you not think they formerly classed a good many as hemorrhagic disease that were not, or that are not classed that way now?

DR SANFORD—I meant to mention that You will find a lot of cases of hemorrhagic disease due to syphilis. I think the big point is that the bleeding time is almost always increased over the coagulation time. If it is increased at least five or more minutes over the coagulation time, it is undoubtedly syphilitic.

DR HELMINA JEIDELL (SALT LAKE CITY) —Is it usually found in only one pregnancy?

DR SANFORD—There have been some cases reported where it occurred in more than one pregnancy but I have never seen it.

DR COOLEY—There is one other subject that might be worth speaking about while we are on this question, that is a procedure I suppose to be common—making clotting and bleeding time tests before operations. My opinion is that those things as ordinarily done are not worth anything and yet it gives people a feeling of safety which I do not think is warranted. If that sort of thing is to be done at all that is where this scheme of Kugelmass' of using a clot index is worth something, because it will uncover things not necessarily uncovered by the ordinary tests. When, for one reason or another, one really wants to have a definite idea whether a patient is likely to bleed abnormally after a tonsillectomy or something of that kind, I think the surgeon and the family doctor should understand that something more than just the ordinary coagulation and bleeding time from capillary blood should be used and I do believe this scheme of Kugel mass' has probably a good deal of value

The meeting adjourned at 4 50 PM

#### Academy News

#### MEETING OF REGION III AMERICAN ACADEMY OF PEDIATRICS

PRESBYTERIAN HOSPITAL, CHICAGO, SEPT 23 1933

(Number present, 28)

#### Dr H F Helmholz, Chairman, Presiding

Motion made by Grulee seconded by Gengenbach that an invitation be extended to all members of the disbanded Central States Pediatric Society to at tend the clinical meeting of Region III. Carried

There was a discussion of the character of the meetings to be held by the Region in the future.

Grulee gave his opinion that the meeting should be mainly clinical.

Veeder after explaining the type of meetings held in St Louis, suggested a one day clinical meeting by clinicans in the city where the meeting is held one day program given over to papers or presentations by men from other cities in the Region

Aldrich thought it was wise to determine how many cities in the Region could entertain the meeting

Rowland states that he always liked to see the interesting cases.

Hamilton especially likes the clinical part of the program.

Irish thinks the important thing is to present practical subjects whether didactic or clinical. He does not think that the demonstration of a patient is always effective in teaching a particular point or subject

Helimbolz summarized that the meetings should be both practical and clinical, that a local committee be given plonty of latitude to draw on the entire Region for men to present the program.

Moved by Veeder accorded by Gengenbach that the matter be left entirely

to the Regional Committee Carried

Next meeting to be decided by the Regional Committee and Gougenbach suggested that the number of sessions at the time of the meeting is a quation to be considered by the Regional Committee

Veeder expressed the opinion that he would like to have the dinners, such as

were held in the Central States Pediatric Meeting continued in the Region.

Aldrich suggested that the clinical meetings be made open meetings.

Grulee thought that the business meeting should be held at the time of the

Gengenbach suggested that if the meetings be open it would be difficult to got a place big enough to hold the meetings.

#### Reports of State Chairmen

Hamilton of Nebraska reported that they have organized a committee in Omaha which is advisory to the schools on all health activities. This committee is very active. It is handleapped by having no money to earry on any work. There is no activity outside of Omaha.

Carson of Kansas—no report Schwartz of Wisconsin—no report

Baxter of Illinois reported that the committee in Illinois has been very active The chief activities include first, a subcommittee appointed to contact and advise with all governmental departments having to do with Child Welfare and Child This committee has secured the appointment of two members of the Academy on the advisory committee of the Illinois State Department of Health Second, a subcommittee has contracted with all nongovernmental organizations ın child welfare This committee has made such contacts and is making some progress Third, the committee has succeeded in the establishment of a Pediatric Section in the Illinois State Society Fourth, the committee has made a policy to conduct all of its state activities through the channels of the regularly or ganized State Medical Society Fifth, the committee has organized state wide pediatric programs, the purpose of which is first, to stimulate the greater interest on the part of the general practitioner in both the well and sick child in order to make the general practitioner more child conscious Second, it is the ideal that eventually there will be no need of any child welfare organizations because of the desire to make every doctor's office a health center The state has been divided into districts more or less corresponding to the Councillor districts of the State Medical Society A chairman has been appointed for each district ings have been arranged for and five meetings have already been held reception of these meetings has been most gratifying and encouraging the winter it is hoped to put on a similar program in each of the Branch Societies of the Chicago Medical Society

Hill of Iowa reported that for two successive years, a pediatric program has been put on at the State Society meeting. A committee has been appointed to coordinate with the work of the State Board of Health with the State Medical Society. Education is the object of both of these organizations. Each county is being organized to appoint a committee on Child Welfare and protection. The Iowa State Medical Society maintains a speakers' bureau.

Winters of Indiana stated that they have organized similar to the Illinois state organization. They have a very close contact with the state government and the work is being definitely supported by the Governor

Gengenbach of Colorado reported that each state has its own problems. They have only five members of the Academy but they have been able to accomplish much through the Rocky Mountain Pediatric Society and by cooperating with the various health departments. The state wide work has been very limited except through some agencies already organized for that purpose

Helmholz suggested that there may be danger in having pediatric sections of our state societies conduct programs for a few pediatricians and not bring these various subjects to the attention of the general practitioners attending other section meetings. At the Minnesota meeting there are several pediatric papers in each medical program

Schorer of Kansas City reported that the pediatric club in Kansas City, composed of about 12 pediatricians, has written the entire regulations for contagious diseases and the regulations for immunization which are a part of the municipal health activities, that no clinic of any sort can be started in the county without the approval of the county medical society. This group has also sponsored and regulated the production of milk and they have gotten everything they have asked for from the authorities.

Miner of Michigan—no work has been done. Two meetings have been held Carey of Michigan

Hempelmann of Missiouri.

Burnham of Ohio had written that they could not be present to report Meeting adjourned

#### Region II

Region II of the American Academy of Pediatrics held a meeting on Wednesday November 15, in Richmond Virginia at the time of the annual meeting of the Southern Medical Association. There was a meeting of the Regional Board on Wednesday morning followed in the afternoon by a joint meeting of the health officers of the southern states and the larger cities of the South. This meeting considered the reports from each of the committees appointed last year Dr John Rührah addressed the joint meeting of the members of the Academy and the Pediatric Section of the South in Medical Association in the evening on 'Arate Anterior Poliomyelitis

#### News and Notes

Dr Harrold A Bachmann of Cheago, Attending Pediatrician at St Luke s and Children's Memorial Hospitals lied of heart disease recently at the age of 42 years

Correction.—Remarks attributed to Dr Alvah L Newcomb of Chicago at the Round Table Conference on Rheumatic Heart Disease, on page 6:1 volume II of the JOURNAL OF PERIATRICS were made by Dr John C McDavid of Oak Park Illinois.

The Central States Pediatric Society held its annual meeting in Chicago, beptember 22, 1933 This meeting was hold in connection with Region III of the Academy of Pediatrics Approximately 200 members were present.

The session on Friday morning was held in the new auditorium of the Chil dren's Memorial Hospital. Luncheon was served at the Michael Reese Hospital and in the afternoon a clinical program was presented by the staff of the hospital Friday evening a dinner was held in Pabat's Cafe at the Chicago Century of I rogress Exposition grounds. At this time a business meeting of the Central States Pediatric Society was held Saturday morning the program was conducted at the University of Illinois College of Medicine

The business meeting of Region III was held at the Presbyterian Hospital on Saturday afternoon with reports of the various state activities. The problems connected with holding a clinical meeting each fall were discussed

At the business session of the Central States Pediatric Society the Executive Committee's Report included two recommendations of general interest

'Recommendation 3 That, whereas there is now a national organization with regional aubdivisions 1.e., The American Academy of Pediatrics, which to a large extent duplicates the activities so ably carried on for many years by our Society and whereas the Executive Committee at our meeting last year in Kansas City were unanimously of the opinion that the Central States Pediatric Society might well be disbunded but deferred action in order that the question might receive more deliberate consideration, the Executive Committee now recommends that this Society be dishanded

"It further recommends that the Society suggest to the Regional Committee of Region III of the American Academy of Pediatrics, (1) that its meetings be conducted as nearly as possible after the manner used by our Society in our annual chinical meetings, and (2) that the members of the Central States Pediatric Society in good standing at the time of its disbandment who are not members of the American Academy of Pediatrics, be invited to attend the annual clinical meetings of the regional subdivisions in which they live

"Recommendation 4 That the balance of funds left in the treasury after the obligations of the Society have been paid be transferred to the Abraham Jacobi Memorial Fund, this being a fund under the direction of the Section of Diseases of Children of the American Medical Association to which all members of our Society either belong or are eligible. It further recommends that the president appoint a committee of three to audit the books of the treasurer and that this auditing committee be authorized and directed to turn over the balance after the obligations of the Society are paid, to the Abraham Jacobi Memorial Fund in accordance with the preceding resolution

"All of the recommendations of the Executive Committee except the fourth were approved as read

"The recommendation regarding the disposition of funds was discussed by several members. Dr Veeder proposed that in making the transfer we specify that in order to perpetuate the name of the Society, some of the money be used to make a medal called "The Central States Pediatric Society Medal" to be awarded each year to some one for special excellence in some pediatric work. Dr Helmholz, Dr Neff and Dr Grulee spoke in favor of this idea

"A motion was made by Dr Grulee and seconded by Dr Helmholz that the money transferred to the Abraham Jacobi Memorial Fund be specified as the Central States Pediatric Society Fund with the suggestion that part of it be used to perpetuate the name of the Society, the manner in which this is to be cone to be decided by the Committee in charge of the Abraham Jacobi Memorial Fund

"This motion was carried

"The original recommendation with this amendment was then approved by

The annual meeting of the Pediatric Section of the Michigan State Medical Society was held at Grand Rapids, Michigan, on September 13 and 14, 1933

Dr Thomas B Cooley of Detroit gave an interesting résumé of the present day conceptions of Blood Dyscrasias in Infancy Dr T Wingate Todd presented a résumé of his work on Bone Age in Infancy which is being carried on at the Brush Foundation in Cleveland, Ohio Dr Louis H Newburgh of Ann Arbor, Michigan, reviewed the recent advances in the study of Calcium Metabolism

The officers elected for the year 1933 34 are as follows

Chairman W A Collins, M D

103 W Burdick Kalamazoo, Michigan

Detroit, Michigan

Secretary Edgar E Martmer, M D 749 David Whitney Bldg

The next meeting will be held at Battle Creek, Michigan, in September, 1934

The regular meeting of the Detroit Pediatric Society was held September 6 1933, at the Children's Hospital of Michigan

The following officers for the year 1933 34 assumed their duties.

President:

J A Johnston M.D

2700 West Grand Blv1, Detroit. E W May M D

\ ice President

1551 Woodward Avenue Detroit.

Secretary Edga

Edgar E Martmer M.D

740 David Whitney Bldg Detroit.

Treasurer E. W Wishropp M D

ool Woodwar! Avenue Detroit

The following appointments have been made to membership in The American Board of Pediatrics.

By the American Pediatric Society

Dr C Anderson Aldrich Winnetka DL

Dr Henry F Helmholz, Rochester Minn.

Dr Philip Van Ingen, New York.

By the American Academy of Pediatrica

Dr Harold C Stuart Boston, Mass

Dr Borden S Veeder St Louis, Mo

Dr Alfred A Walker, Birmingham Ala,

By the Section on Pediatrics of the A. M. A.

Dr Wilburt C Davison, Durham, N C.

Dr Franklin P Gengenbach, Denver Colo

Dr Edward B Shaw San Francisco Calif

The Board is in the process of organization and incorporation. Announcements in regard to the Board will appear in The Journal of Pediatrics and The American Journal of Discases of Children.

#### Book Reviews

The Diagnosis and Treatment of Postural Defects. W M Phelps and R J H Kiphuth, Charles C Thomas, Springfield, 1932, pp 180

This monograph is the best one on the diagnosis and treatment of postural defects that has come to my notice. The material as well as the manner in which it is presented and illustrated leaves nothing to be desired. It can be recommended to all students of the subject and the knowledge contained in it should have far wider application especially in the physical education depart ments of our schools. If only teachers of physical education realize that—

- (1) The term "flatfoot" is very misleading,
- (2) That forward shoulders in children is related to the prominent abdomen and is rare during the adolescent period,
- (3) That there should be no attempt to localize lumbar correction in children because of the danger of compensatory defects due to flexibility,

much wasted effort as well as considerable harm would be prevented

Chapter I on evolutionary influences will repay anyone for careful study While one must, as the authors frankly admit they have done, draw upon his faculty for imagination when he attempts to understand the many and varied steps by which man has arrived at his present development of the upright posture with bipedal locomotion, there is no other method of analysis which so satisfactorily serves as a basis for study and didactic teaching. The reconstruction of evolutionary influences with the realization that gravity is the principal force in the maintenance of good posture with a minimum expenditure of muscular energy lay the best foundation for more detailed study and a clearer understanding of body mechanics

On the subject of environmental influence I cannot entirely agree with all the ideas expressed by the authors. The study of this chapter gave me the idea, perhaps mistakenly, that the authors have not studied the natural changes in posture that one sees in the observation of individual children during the whole period from infancy to young adult life. While the study of many individuals in age groups yields invaluable information, it is only by the continuous observation of individuals as each grows up that one learns to predict his future development. Such study is the basis for the following suggestions.

Every normal infant is bow legged until after he has walked for a few months. The authors suggest too early walking as a cause of bowlegs. All children go through a period of physiologic knock knee with pronation of the feet accompanied by a stretching of, or a lack of development of the heel cords which permits dorsal flexion of the feet well beyond a right angle. This stage of knock knee and pronation of the feet reaches its height at age three and is sufficiently corrected by age five or six to be of no consequence. The correction is accomplished, I think, by the development and better coordinated use of the external rotators of the thighs and of the gluteals. The authors mention both the pronation of the feet and the knock knee but do not sufficiently emphasize them as parts of normal development. Failure to recognize the physiologic nature of the normal amount of pronation in the feet of young children has given rise to the widesprend practice of attempting to correct it by means of advancing and elevating the inner borders of shoe heels (Thomas heels) and worse still by clovation of the inner borders of the sole as well. These mistaken attempts at cor

rection contribute considerably to the unnatural shortening of heal cords and very probably to the development of rigid contracted foot. In turn this shortening of the hool cords contributes the undesirable effects higher up so well described by the authors on page 15. When the child is about six years old if pronation persists, it may be safely corrected because the child will then have lost some of his natural flexibility as well as have acquired such a degree of muscular development and general coordination that he can better distribute and utilize the effect of the correction. The argument is in line with the authors well-defined and wise warning that posture training should not be begun too early in the child's life because of the danger of overdevelopment of certain muscle groups.

The importance of shoes and stekings is well emphasized. Anyone who has observed the deformities produce I by tight stockings and badly fitted shoes, especially the shoes that are fitted or worn until they are too short, can have no doubts concerning the attention that should be given to these articles of apparel. I cannot agree with the authors also that 'a moccasin is innecessas when worn on a normal foot.' A moccasin is I am certain the only form of shoe for normal infants until the full development of skillful coordinated walking which does interfere with the best development of the muscular power and functional skill of the feet. Why should the feet only be set aside as the part of the body to which support should be applied as a preventive measure? The advisability of support for the feet depends upon the individual case just as the authors point out in discussing shoulder braces and abdominal supports in another para graph.

The authors' conclusion the environment factors in the posture of the well pre-school child are therefore confined chiefly to the feet ' if accepted literally will produce in one s mind a conception of body mechanics which is not in ac cordance with physiologic facts. The feet are only part of the whole mechanics of the body concerned in bipedal stance and locomotion. An imbalance produced by deformity of the feet must be counterbalanced by a deformity or at least a deviation in the opposite direction in some other part of the body. Conversely a deformity or deviation in some other part of the body may have its opposite compensating or balancing deformity in the feet. Correction of the foot deform ity if properly done will have a beneficial effect on the general body mechanics. However if the foot condition is thought of too exclusively of its relationship to the rest of the body harmful overcorrection may result.

CLUFFORD SWEET

The Early History of The Infant Welfare Movement. G F McCleary London 1033 H K. Lewis & Co pp. 176

An interesting and readable account of the origins of the Infant Welfare Movement. While dealing chiefly with the movement in England, the discussion of the French influence is adequately covered. The author stresses the importance of the early work of Dr Nathan Strauss and Dr Henry L. Colt in America and the emphasia placed upon milk. We recommend the reading of the book by the younger pediatricians who step into work in the fully developed welfare center of today

BORDEN VERDES.

Therapeutique Hydro climatologique en Pédiatrie P Nobécourt and G Boul anger Pilet Paris Masson et Cie, 1933, pp 195

A discussion of the indications for hydrotherapy and climate in various conditions in infancy and childhood. A list of the principal thermal and climatic stations in France is given

B S V

The Clinical Study and Treatment of Sick Children. John Thomson and Leonard Findlay Edinburg Ohver and Boyd, 1933, pp 1075

A fifth edition of Dr Thomson's well known textbook by Dr Findlay The revision is excellent and in keeping with the high standard set by Dr Thomson in the first edition some thirty five years ago

B S V

#### Comments

FROM reports we have heard and until un of the minutes of the recent Child Health Recovery Conference all 1) | 1 | (hillren's Bureau') and held in Washington on October 6 the impression of the interested observer that some one became quit in 1011 5 or the fact that many children in the precent period of economic his in 1 or vinton were not getting sufficient food to keep them in good health of term home, hungery. Therefore, something should and must be done about it. With it in one can liengree. It is a question of necessary rolle?

The proposition that we outh it and a group called to Washington to adopt was a nationwide examinate it interest for malnutrition, this to be carried out by the respective states under the gineral for malnutrition, this to be carried out by the respective states under the gineral guidance of the Children's Bureau. This is quite a different matter. The lass error, of course lies in thinking of malnutrition and insufficient food make in all the same thing. That insufficient food make lead to malnutrition if continued it is a long period in, of course, a fact. Up to the present time at least in afficient food has been one of the more rare and un common causes of malnutrition. Where food has been a factor in malnutrition, it has been associated with faults of a habits, unbalanced diet and the like rather than with a lack of food. The common causes of malnutrition are found chiefly in disease, physical defects fatigue, and faulty habit formation.

It should not be difficult through our regular sound agencies who are handling relief, to find those children who actually are getting too little food. Give them the food. Do it rapidly and at one and elaborate medical examination in blanks furnished by the Children's Bureau is shooting rather wildly into the air

What, it may semonsly be asked does the government propose to do? If mal nutrition is the goal, does the government intend to provide convalescent homes for the thousands of malnourshed children with an underlying cardiac or tuberculous lesion, or bloody holidays when tousits and advands are removed by the thousands If "malnutritian" as shown by a medical examination is the basis for giving extra food to hungry children who need it the only logical thing is for the government to provide relief for children malnourished from other causes. It is rather an absurd situation.

From a more practical standpoint as physicians we must tak first of all what standards are to be used. It has taken years and will continue to take years to over come the minuse and misapplication of height weight age tables of measurement as applied to malautrition. This if we recall it correctly was largely the result of the measuring and weighing campaign of the Children's Bureau. There is danger of "food and malautrition" being linked together in the minds of the larty as one and the same thing if a "malautrition" campaign on the basis outlined is made a propaganda movement by the Children's Bureau.

We are strongly in favor of food relief for children who need it. We are further in favor of the careful medical study of malnourished children and the application

of indicated remedial measures. This latter is a time taking process and a continuous need, and one which is under way in many of our cities and in some of our states. For example, the work in Pennsylvania was outlined by Dr. Hamill in his recent presidential address in the September number of the Journal. We feel, however, that the conference in Washington exhibited a lot of loose thinking and mixed up some simple direct things in a complicated unnecessary way.

This is an expression of personal reaction and opinion. Doubtless, many will disagree This column, as has been stated several times, is an open forum for the discussion of pediatric subjects and is open to those who hold opinions which differ Quite obviously with such a purpose in view, it cannot be regarded as the "official voice" of the Academy of Pediatrics Academy discussions and actions are printed under the head of Academy Proceedings

BEGINNING with the January number, the Journal will make a past to present change. The interesting series of eighteen articles on Pediatric Antiques by Dr Drake of Toronto will end with the present number. In January the first of a series of articles on "American Pediatric Clinics" will appear. Twelve outstanding clinics have been selected by the Editorial Board. Although there has been some objection on the score of "modesty," the Journal has requested that the individual clinics be described by the Chief of Staff or someone who has been in timately connected with the clinic for a number of years rather than by an outside reporter. The scope of the articles will include the history and aims of the clinic, physical and clinical facilities, house officers, and research facilities. If the series is as interesting as the Editorial Board expects, it will be followed by one on foreign pediatric centers. The Editors wish to take this opportunity to express their thanks to Dr. Drake for the time and study he has given to the series of special articles closing with this number.

WELCOME the first number of the Indian Journal of Pediatrics, published in Calcutta The Journal, which is to appear quarterly, is published in English and is edited by K. C. Chaudhuri. The first number contains a foreword by Sir Nilratan Sircar, a Birthday Greeting by Dr. Robert Hutchinson, and an Introduction by Czerny. The contents contain several original articles, society proceedings, book reviews and abstracts. May it live and prosper.

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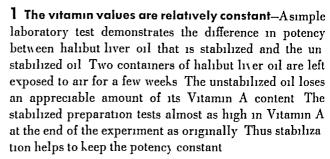
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## THE JOURNAL OF PEDIATRICS

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The over-solicitous or too-sympathetic mother psychologically conditions her child against cod liver oil when she murmurs "Oo poor dear! Muvver's so sorry oo must take this nasty old medicine" Children are quick to sense the parents' attitude and to take advantage of it Sympathy, disgust, or anger on the mother's part all militate against her child's taking cod liver oil and in effect may result in (or at least fail to prevent) rickets, tetany, and other calcium-phosphorus disturbances in her child—for which cod liver oil is prescribed There is, therefore, good clinical reason for the physician's taking a personal interest in "cod liver oil psychology

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Some of the factors that interfere with the physician's clinical judgment are psychologic in nature, as suggested by the accompanying pictures Other important points worthy of the physician's personal check up with mothers are

1. Is the teaspoon standard size? The stand ard teaspoon has a capacity of 1 fluid

Is the oil given in an emulsion or mix-ture? If so only about one-third of the dose is cod liver oil.

3 Is the oil administered with cereal milk, or other foods? Part of the oil clings the serving utensil and allowance should be made for this loss.

Is the oil kept cold? Chilling the oil makes it virtually tasteless.

In the vitate" really from the oil or from a metal spoon? Silver or silver plated spoons often produce a disagreeable taste not present if a glass spoon is used

6 Does the mother permit the older child to measure out his own cod liver off. Children often bring their ingenity to bear in trying to evade the medication.

7 Does the baby actually spit up the oil as the mother sometimes states, or does it merely fail to swallow all of it? If the mother will place the baby on her lap and hold the childs mouth open by gently pressing the cheeks together between her thumb and fingers while she gives the oil, all of it will be taken.

8 Is the oil palatable and of low acidity?
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#### The Journal of Pediatrics

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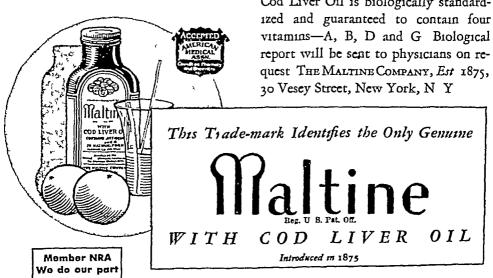
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Official Organ for THE AMERICAN ACADEMY OF PEDIATRICS

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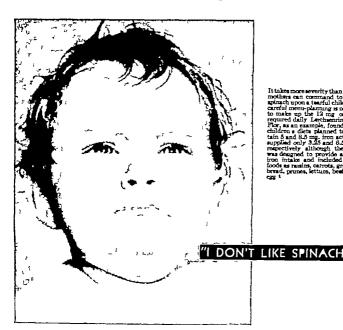
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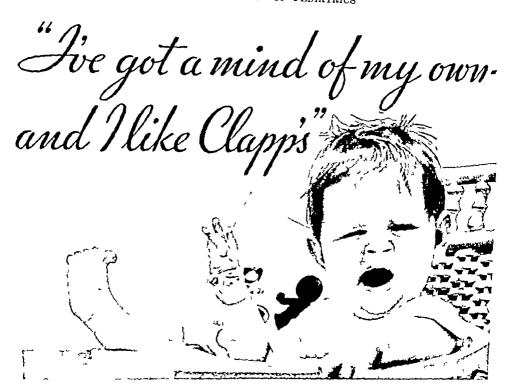
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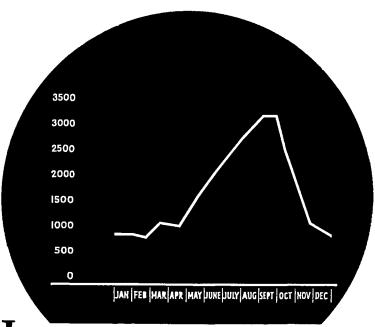
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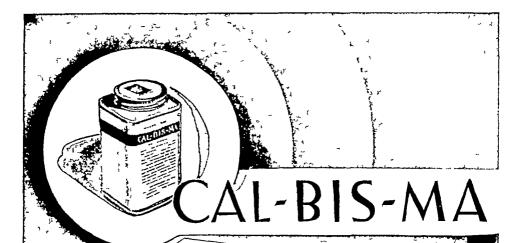
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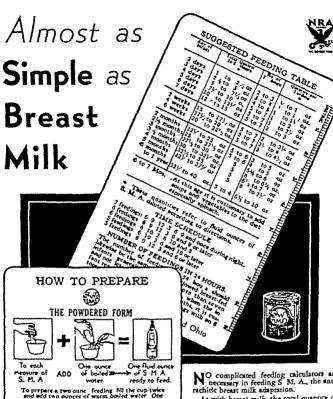
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To un may send me a sample of Gerber 3 Strained description the send me a sample of also analysis and description to the organization of the Strained Vergetables as filed for acceptance with the Organization of the American Medical Association of these products as filed for acceptance and Some Norsa Foods Committee of the American Medical Association of these products are palms of the American Medical Association of the Am 15c at Grocers and S Committee of the American Medical Association.

Bookles, Baby's Vegetables and Some Notes on
Mealtime Psychology Druggists

**Z**o

# Why CARITOL?

- 1 For ages, man has eaten certain palatable fruits, vegetables and dairy products to satisfy his hunger
- 2 His body requirements for vitamin A were thus un consciously satisfied in greater or less degree
- 3 The substance responsible for this vitamin A activity has recently been shown to be carotene, a yellow organic pigment [C40H56] called Primary Vitamin A by Sherman & Smith in 1930
- 4 The prevalence of latent vitamin A deficiency diseases suggests to numerous investigators that modern diets do not contain enough carotene to fully satisfy the requirements of many individuals.
- 5 The fact that carotene is normally present in various parts of the body such as the spleen blood lymph breast milk, corpus luteum, placenta, ovaries, suprarenal glands and bone marrow would seem to indicate that in addition to its activity as a vitamin, carotene itself meets other body requirements besides its conversion into the colorless product by the liver
- 6 If this deficiency is to be made up, what is more natural than to supply the same palatable substance carotene, derived from vegetables, in concentrated form?
- 7 This is now possible. A highly potent solution contain ing 0.3% carotene [Primary Vitamin A] in oil is offered to physicians as Smaco Caritol, available at most pharmacies.
- 8 Caritol literature may be obtained from S M. A. Corporation, Cleveland, Ohio.



# Information about Karo Syrup Which Will Interest All Physicians —

# Particularly Pediatrists

In response to numerous requests from physicians, Corn Products Refining Company is pleased to publish the following analytical data about Karo Syrup (Blue Label)—which has proved so effective in the feeding of infants

The following acceptance of Karo (Blue Label) by the committee on foods, appeared in Journal of the American Medical Association, January 23rd, 1932

The product is a mixture of corn syrup with a relatively small amount of re finers' syrup The refiners' syrup must be acceptable in flavor and color and fulfil the U S Department of Agriculture standard for that product, "Refiners' Syrup, treacle, is the residual liquid product obtained in the process of refining raw sugars, and contains not more than 25 per cent of water and not more than 8 per cent of ash"

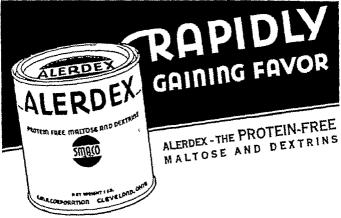
The corn syrup is manufactured by hydrolysis of high grade corn starch in dilute hydrocloricated suspension. The mixture is heated under steam pressure until chemical tests indicate the desired degree of hydrolysis. The resultant mixture is almost completely neutralized with sodium bicarbonate and filtered through white linen filter cloth, the filtrate is passed through a deep bed of animal charcoal for decolorization and deodorization. The final filtrate, which is water clear and odorless, is concentrated under reduced pressure to a density of 138 (20 C 120 C)

### CHEMICAL COMPOSITION

	per cent
Moisture	25.3
Ash	06
Fat (either extract)	00
Protein (N \ 6.25)	0.2
Dextrins (by difference)	37 1
Maltose (method of Wesener and Teller J Indust & Engin	ı
Chem 7: 1009 1916)	22.2
Dextrose (method of Wesner and Teller J Indust & Engire	
Chem 7: 1009 1916)	7.5
Sucrose	4.8
Invert Sugar	2.3
Titratable acidity as HCl	0 025

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### WHY IS ALERDEX PROTEIN-FREE?

 Since certain proteins are frequently the cause of eczemas and other forms of allergy it is desirable to eliminate these offending proteins from the infant diet. Cereal proteins are frequently present as contaminants in some milk modifiers The routine use of a protein free carbohydrate in all milk modifications should help to diminish the incidence of these troublesome eczemas. Alerdex is a protein free carbohydrate developed by our Research Division to meet this need and the demand for it is steadily increasing

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#### CHARACTERISTICS OF ALERDEX

- ! Helps prevent eczemes when used rout inaly due to absence of offending protein.
- 2 Use present formules because Alerdex has same caloric value and percentage of maltons and dextrins.
- 3 Does not take on exposure to air because it is non-hygroscopic.
- 4 Directives readily in warm water or milk.
- 5 Snow white, free-flowing powder
- 6 Inexpensive—in spite of extra processing under technical control, costs no more.
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#### APPROXIMATE ANALYSIS OF ALERDEX

Alerdez is resentially a mixture of approximately qual parts of malture and destrine. It is prepared by a new thermally-cost olled y seem of the ennie hydrolysis of nen cereal starch, as a result of which it contains no gratein contaminant

Moleture	30
Ash	0.3
Pat (etha extract)	0.9
Hydrolyzed protein (N x 5.45)	Ø 05
Reducing ong 18 au maltage	50.0
Dextrin (by difference)	45.6
Level tublespeons, per ounce	4
Caleries per lavel tablespoon	27%
Calories, per sence	110

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Sodium Taurocholate 1/4	gı
Phenolphthalein 1/2	gı
Extract Cascara1/2	gr
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Allergic manifestations caused by food may take any of the following forms

- ECZEMA, especially in infants caused by ordinary milk.
- GASTRO ENTERIC DISTURB ANCES, as vomiting, diarrhea constipation
- HYPERACUTE TYPE with urticaria, asthma and symptoms of shock.
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Can be used indefinitely because all essential food elements of milk are still present.

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Convenience Individual feedings may be made up for infants.

Lower cost Powder form costs 25% less than liquid

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(nitrogen) to pre vent deteriors tion.

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This twenty-two page booklet has proven popular with the medical profession. It contains a brief resume of current literature on Milk Allerny, quoting fifty-one authorities prepared especially for Physicians. Bend the coupon for a compilmentary copy of the fifth edition.

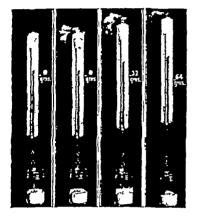
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□ Trial pockage Hypo-Allergic Whole Milk (powder) 20-93 □ Milk Allergy booklet with bibliography (For samples and literature without obligation amply attach to prescription blank or letterhead.)

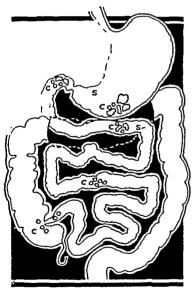
# CURD TENSION - AND INFANT FEEDING -

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# **PROTEINS**



BREAST SIMILAC POWDERED COW S MILK MILK MILK



C—Cows milk S—Similac Schematic drawing of the relative size of the curds of cows milk and Similac vom ited by six weeks old puppies after one half hours ingestion.

THE most available and the most easily digestible form of protein for infants is the protein of milk. The protein of breast milk is more digestible than that of cow's milk."

"In the light of our present knowledge, the chief cause of the difference in the digestibility of the protein of human milk and that of cow's milk lies in the greater proportion of casein in cow's milk"

"It is the formation of large curds which renders the casein of cow's milk so much more difficult of digestion by the infant than that of human milk. If the formation of large casein curds in the stomach can be prevented, the casein of cow's milk is easily digested" 1

In Similac the large casein curds are not formed. The curds formed when the gastric enzymes act upon Similac are small and flocculent, registering zero on the tensiometer, as shown in the illustration, hence more easily digested

The finer the curd the greater the surface area The greater the surface area the more exposed are the fats, carbohydrates, proteins and salts to the digestive enzymes Result .. a more complete utilization of the food elements

<sup>2</sup>Morse and Talbott, Diseases of Nutrition and Infant Feeding, pgs 214, 215

Samples and literature will be sent on receipt of your prescription blank

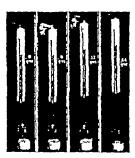
SIMILAC-Made from fresh skim milk (casein modified); with added lactose salts milk fat and vegetable and cod liver oils



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emails drawing f the relative size of curds of caw rallk and Similes vem-by six weeks old puppies after one-

THE mineral solts play a very complicated part in digestion because they are not only absorbed by the intestines but also may be re-exercted into the digestive canal"

"The mineral salts are of even greater importance in infancy than in later life because of the rapid growth of the bony The salts are also necessary for cell growth and are important constituents of the blood and digestive juices, facilitating secretion, absorption and exerction."

Some of the important mineral salts are encased within the large tough curds formed from cow's milk, and only those salts that are not encased in the curds are available for metabolism.

The curds formed from SIMILAC are small and flocculent, registering zero on the tensiometer as shown in illustration, hence the mineral salts of SIMILAC are available for metabolism.

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Mores and Talbet Discuss of Natrition and Infant Feeding, pg. 59 Marriett Infant Natrition pg. 43

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### Is that the brand of Evaporated Milk you would have chosen?

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Where Diarrhea is either continuous or intermittent, and as many as 20 to 30 stools daily may be passed—stools which always contain the pathologic triad of feces, that is, blood, mucus and pus, and frequently consist almost entirely of this material—

Where Varying With Severity, the condition may grow progressively worse to debility and emaciation, with progressive anemia and irregular periods of pyrexia and where death from the condition is not at all infrequent—

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"I put the baby on small quantities of Dryco, full strength, and gradually increased the amount of each feeding as the child improved and could take more No vomiting occurred after the dextrose and buffer salts were given With three days of Dryco feeding, the stools became of a normal consistency and were free of mucus. The appetite rapidly returned" (Arch Pediat, Vol. XLIX, No 2, Feb., 1932)

DRYCO is digested and assimilated when other foods fail and because of the added vitamin D content, babies receive automatic protection against Rickets, the most common nutritional disease of infancy and childhood

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Of course, PMC is not only a calcium source Derived

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wholly from milk, P M C contains the other essential salts of that "most nearly perfect food" Its full composition is lactose, non-casein soluble milk protein and chlorides, phosphates and citrates of potassium, calcium, sodium and mag-The higher concentration of lactose and milk minerals in P M C suggests its definite use as a special dietary food where the child's mineral intake is insufficient-3 tablespoons give approximately 1 gram calcium

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has been prepared a Portfolio in which is summarized the latest information on the subject of proper shoes for babies to four years of age. It is a

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in which the Department of Medical Co-operation has assembled in convenient form for constant reference, what Research has developed in recent years References are quoted

Illustrated with reproductions of X-ray photographs and studies, it contains information about shoes which are designed to aid the profession in preventing improper foot developments

This Portfolio will be mailed without charge to members of the profession upon request. Just write on your letterhead or prescription blank to

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A Mineral Oil and Cascara Sagrada Emulsion with a

# Lessened Tendency to Leakage

WHILE regarded by the medical profession as a valuable intestinal lubricant, mineral oil has certain disagreeable features - notably the tend ency to rectal leakage - which limits its use.

More than a year ago tests were begun in the Maltine research laboratories to evolve an effective emulsion which would retain the advantages of the mineral oil and at the same time climinate the objectionable features. MALTINE WITH MINERAL OIL and Cascara Sagrada is the result.

This mineral oil is incorporated with the Maltine by a special vacuum process by which the mineral oil is broken up into very minute particles. Laboratory and clinical tests cover ing a period of many months have shown that this combination is superior to the plain min eral oil in taste and appearance. The tests also indicate that the new emulsion lessens the tendency to leakage because of the finely divided nature of the oil present and the small dosage required

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# HIGHLIGHTS on Ultraviolet Irradiation in the treatment of ERYSIPELAS

Many physicians have found ultraviolet so valuable in the treatment of erysipelas as to regard it as a favorite modality. Technique varies, some using only the air-cooled Alpine Sun Lamp, others preferring local applications with the water-cooled Kromayer Lamp, followed by general irradiation by the Alpine Sun Lamp.

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"One hundred forty-seven cases were treated with ultraviolet irradiation." "The best average results were obtained with ultraviolet irradiation." "Comparison of the individual methods of therapy 8 h o w s the lowest mortality rate in the ultraviolet series." "I dare say that no one will deny that ultraviolet radiation is the method of choice"

Walter H Ude MD Minn Gen Hosp Archives Phys Ther X-Ray Rad Jan. 1931

\* \* \* \* \*

"Ultraviolet irradiation produced a clinical arrest of the disease with the first treatment in 92 per cent of our cases" "(It)has none of the objectionable features of the other methods, while it seems to excel them in effectiveness We are now using ultraviolet radiation in all of our cases of erysipelas"

W H Ude MD and E S Platou MD, Jour AMA. July 5 1930 "In the series of (51) cases to be described the source of ultraviolet light was a standard model aircooled quartz lamp" "The cases treated ranged in age from 7 months to 74 years, and included 'primary' cases and cases secondary to accidental wounds, operations, and confinements As usual there was a marked preponderance of facial cases" "The forty-seven cases treated and ending in recovery were of varying degrees of severity"

J M Davidson M D D P H Edinburgh Brit. Med Jour May 21 1932

"Good results have been obtained in this disorder with both x-rays and ultraviolet rays"

George M MacKee M D Jour A M A. April 30 1932

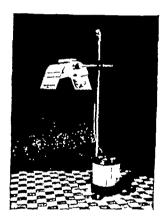
"Clinical evidence of the value of U-V irradiation in erysipelas is amply available to all who take the trouble to study the literature on the subject before pronouncing an opinion"

R. King Brown MDDPH Editor Brit.
Jour Actino & Physio
Sept. 1030

"The most remarkable results have been obtained in erysipelas (six patients), all of whom recovered"

John Zahorski M D Am Jour Dis Child Jan 1925

The Hanovia Company guarantees the ultraviolet out put of its lamps. It makes no claims for the therapeutic results of ultraviolet, but an extensive library on the subject is maintained, covering over 25 years of practical application, from which the Company is glad to inform you what clinicians and research workers the world over have reported on any disease in which you may be interested



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"when an infant is deprived of breast milk and has demonstrated an inability to tolerate cow's milk, or when fresh cow's milk of unquestionable purity is not available, the powdered whole milk as produced by a spray process meets a greatly needed demand"

(W Va Med Jour, 28 193 240, May, 1932)

### The U S Department of Agriculture Stipulates

"I quart of milk daily from early childhood to adoles cence and I pint or more daily for the adult When shortage of money forces the expenditure for food to an abnormally low level the proportion spent for milk should be increased. (Amer Jour Pub Health, April 1933)

## Advantages of KLIM Powdered Whole Milk

- Clean, safe and uniform milk supply for patients of all ages
- 2 A most digestible form of milk—fat is broken up and protein made more diges-
- tible through process of
- 3 Requires no refrigeration
  —always fresh and ready
  for use
- 4 No wastage

SAFE, PURE WHOLE MILK IN POWDERED FORM





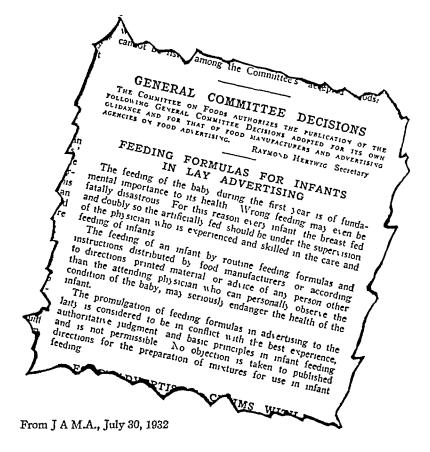
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# The Journal of Pediatrics

Vol. III

SEPTEMBER, 1933

No 3

## Original Communications

# PRESIDENTIAL ADDRESS AMERICAN ACADEMY OF PEDIATRICS

S McC Намил, M.D Рипаредения, Ра.

IN HIS admirable presidential address delivered at our meeting a year ago, Dr Morse set forth most beautifully and comprehensively the relationship that the Academy should bear to the health and wel fare problems of the child and the unusual opportunities offered us as its fellows to render a high service to humanity. I would like nothing better than to repeat the substance of his address but it is not in my power to handle it with the skill and finesse that did Dr Morse.

The Academy is just emerging from the tender age of infancy and is celebrating its third birthday. Despite its youth it can point with definite pride to some real accomplishments or, perhaps one might better say, to very definite progress which augurs well for future accomplishment

It may not be amiss therefore, to stop for a moment to consider how far we have traveled

The Academy came into being just as the White House Conference was completing its labors. The Conference undertook the prodigious task of ascertaining what was being done throughout the country for the health and protection of the American child, what were the gaps in the program and how these gaps could be filled. The first two of these objectives were reasonably well covered but the third from lack of time was sourcely touched.

However one very vivid fact that impressed itself upon the par ticipants in the Conference was that, if we could bring about a full and intelligent application of the knowledge we already possess, the gaps in our program for the health and protection of the American child would be considerably reduced Due to the clear vision of our secretary in laying the foundation for its activities the Academy has builded well to meet this important need

We have created a number of committees which, functioning properly, should have an important educational influence in the fields they represent. They should make themselves fully conversant with their subjects and make that knowledge available to the agencies working in these various fields throughout the country. Although time does not permit a detailed consideration of all the committees I would like to draw your attention to outstanding features of the work of certain committees, the need for alteration of purpose or nomenclature for others, and future opportunities for still others. The Committee on Pediatric Education has done an admirable piece of research in its field, which it is continuing and which is being made of practical value to the medical schools of the country.

The Committee on Hospitals and Dispensaries issued a most searching and valuable questionnaire to the children's hospitals of the country. Through the interest and cooperation of the Fellows of the Academy all of these questionnaires save one have been returned fully answered. It is the first time such complete information on this subject has ever been assembled. This material is being tabulated and studied. From it will evolve a picture of the children's hospital situation which will enable us to evaluate the services of these institutions and be better qualified to advise intelligently regarding them

As Dr Morse said in his address, "Committees are of no use unless they do something"

Some of our committees have a rather limited field of action and it might be worth while for the Executive Board to consider whether some of them may not be advantageously eliminated. There is probably no further use for the Committee on Relations with the White House Conference. The Conference has ended and its follow-up committee has disbanded. However, under a somewhat altered title it might well serve a useful purpose. There was a vast amount of valuable information collected by the Conference. Unless someone carefully reviews the transactions of that Conference and extracts the material that has practical application, there is grave danger that it will remain buried in the tomes which embody it and never be put into action.

There would seem to be a very important service for the Committee on School Health and School Health Education Both of the subjects included in this title are under criticism. We all know how inadequate is the health supervision of the school child the country over. We also know that this service is under severe criticism by the rank and file of the medical profession on the ground that it infringes upon the prerogatives of the physician.

There certainly should be some agency engaged in a study of this entire problem to determine its objectionable features and evolve a plan by which they can be overcome

There is a prevalent impression that education in health, as given in our school systems is unsatisfactory. To determine whether this impression is justified should be our function. We certainly should know whether instruction in the important subject of health protection is being intelligently and effectively carried out in our school systems.

The Committee on Mental Hygiene would seem to have not only an important but extremely interesting function. The question of the training a medical student should receive in psychiatry to enable him to cope with the behavior problems he will meet in practice, a study of the misleading literature that is being fed to young mothers and the means of combating its disturbing effect and many other interesting points offer opportunity for this committee to do an effective work

The Executive Board might also consider whether its committees are founded on the most efficient and effective basis possible. There are two kinds of committees which usually function well. One that is headed by a chairman who has a full knowledge of and is vitally interested in, the subject the committee is created to consider. In such committees most of the work, however is done by the chairman. The other is the local committee which has opportunity to bring its membership together frequently.

Committees of national organizations whose membership is widely scattered and who are without salaried executives if dealing with sub jects requiring constant and continuous consideration, are rarely ef feetive The work of the Academy committees is continuous and their membership widely scattered. The purpose of this latter point is easily evident. The Academy naturally desires to stimulate the interest and use the knowledge and ability of all of its members a very important consideration-but from the standpoint of getting work done I am not sure the present committee plan is wise. Is it not pos sible to accomplish the desired result by increasing the membership of these committees, retaining an adequate geographic distribution but at the same time selecting in the community in which the chairman resides a group of four or five members who can get together fre quently and support and advise the chairman? The results of the studies of the local groups could readily be submitted to the other members for review and criticism

I believe further that it would be well for the Executive Board to consider the advisability of granting each of its committees a small stipend for occasional secretarial work and necessary postage such an allowance to be based on evidence of serious activity on the part of the committee

If such a course, or some other modification of the present plan, is followed and committees still fail to function, it would seem that the Academy should give careful consideration to the advisability of using other avenues through which to accomplish its purposes

Our admirable Journal, which has had an almost unprecedented career in the first year of its existence, constitutes an excellent medium through which to extend our educational function

May it not be possible for the Journal to lay more stress on the social aspects of medicine? The fields of sociology and preventive medicine are so interrelated and each dependent so much on the other that it has seemed to me we might advantageously use the columns of the Journal for freer discussion of these interrelated problems. Can't we also lay more stress upon the protection of health? The studies of the White House Conference showed a woeful lack of application of protective procedures. They report that a very small percentage of the children had been vaccinated against smallpox or protected against diphtheria, and still fewer had had health or dental examinations. Certainly we are the logical body to popularize these important procedures and the Journal should be a useful medium for accomplishing these results.

It was stated in the first issue of the Journal that "it is the intention of the editors to make it as broad and inclusive as the field of childhood itself"

We cannot expect the editors alone to attain this much desired goal. There are certainly many members in the Academy who are interested and experienced in these fields who could and should contribute. There are also many outstanding men and women in the social workers group who are keenly interested in the medical aspects of their problems and who could be induced to contribute to the columns of the Journal

I am wondering whether the members of the Academy have responded as fully as they might to the appeal of our editors for material for the section of the Journal reserved for "News and Notes". I know that it has been the hope of our editors that this might become a very useful and interesting column. I would like to urge upon you the importance of doing everything in your power to make the Journal what I believe it can and should be, the most interesting and helpful forum for pediatric discussion in the country.

As I have reviewed, with great interest, the activities of Region II and those of the various state committees that have organized, I have become convinced that the regional and state committees offer a most effective avenue through which to accomplish many of our aims and purposes

There are certain very definite needs we must meet and a number of obstacles we must overcome in the field of practice. The public is demanding that active measures be taken to protect the health of children. Dr Morse has pointed out that the public 'will see to it that they are taken'. As a matter of fact they are 'seeing to it'. The majority of us have been indifferent to this trend

Our preventive clinics, our health centers, our state and municipal health departments, and to a less extent our hospitals, all of whose free services should be entirely restricted to the care of the indigent are daily opening their doors wider to those who can afford to pay

The medical profession is largely responsible for the fact that our potential pay patients are taking unfair advantage of this. We have been fully conscious of the fact that for years the public has been plied with propaganda urging upon them the importance of health protection. This propaganda has come from sources they respect and the public has been waiting for the physicians to offer them this protection. The profession at large has not equipped itself to render this protection and those who are prepared have not had the courage to urge the value of health examinations and the importance of preventive procedures. The natural result is that the public has sought these services where they can be had

We naturally object to this procedure but what are we doing about it? Aren t we merely standing on the sidelines and futilely shouting our protests? Have we developed a plan to check this trend?

The Academy through its state committees has an unusual opportunity to put effective plans into action. The New Jersey committee has adopted a procedure which promises to be most effective. After careful consideration Pennsylvania decided to copy this plan with certain modifications. For illustrative purposes I shall refer to this Pennsylvania plan in some detail.

It calls for a state committee with county units to be under the auspices of the state medical society. The officers and trustees of the Medical Society of the State of Pennsylvania were overtured by the Pennsylvania Academy Committee with the request that they accept the responsibility of creating such committees in Pennsylvania

About this time the Governor of Pennsylvania called a conference in Harrisburg to consider the best means of combating the rapidly increasing malnutrition among children that was being reported to the Emergency Rehef Board which at that time was feeding 450 000 families including almost a million children

At this conference a member of the Academy Committee, having in mind the proposal put before the state medical society suggested that a state-wide Emergency Child Health Committee with county units be organized at once. This proposal was adopted and the stage was immediately set for carrying out the program that had been submitted to the officers and trustees of the state society.

A Planning Committee was organized, having in its membership the president, president-elect and secretary of the state medical society

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There are certain very definite needs we must meet and a number of obstacles we must overcome in the field of practice. The public is demanding that active measures be taken to protect the health of chilstrict their services to the definitely indigent groups. This calls for a new attitude of mind not only on the part of the agencies but also on the part of physicians The latter must be prepared to render the services in health protection to those who, they believe, should be re fused this service by the clinics. This will probably entail an adjust ment of fees to meet the economic circumstances of this group of the first important points to establish is the economic basis on which free treatment should be refused. This is a wholly unsettled point but one which these county committees, with their varied representa tion, should be able to determine They can also develop a plan satis factory to the medical profession for the economic rating of those who are refused free treatment so that they may be referred to their physicians with a definite recommendation as to the fee to be charged. Such a system is in action in the Philadelphia schools in respect to eve pa tients and is working very satisfactorily. It was put through under the auspices of the Philadelphia County Medical Society tions we have had from physicians in several of the counties of Penn sylvania have convinced us that such a plan is feasible and would be acceptable

As has just been said, the physician must be equipped to make the necessary health examinations and to apply the essential protective procedures. We dare not put ourselves in the position of objecting to the giving of a service by others which we ourselves are not prepared to render.

This point has been taken into consideration in the development of our work in Pennsylvania. Realizing that a health examination must be the basis on which to determine the health and nutritional status of the children we are called upon to protect, the Pediatric Advisory Committee has prepared a health examination form which is officially endorsed by the state medical society. It is so formulated as to require consideration of the entire child. We feel that the making of these examinations by many physicians will have a very definite educational value. To supplement this educational feature we have prepared an explanatory leaflet which is given to each examining physician. In addition we are sending pediatricians to the County Societies that request it to discuss with them the subject of health examinations

The State Committee of the Academy is at present engaged in for mulating a plan for definite courses in preventive pediatrics to be put into operation in the autumn.

We hope through these various avenues not only to equip the physician for this service but also to stimulate his active interest

There have been two developments in the course of the emergency work in Pennsylvania that are especially gratifying. One is the eager ness with which lay organizations and individuals have accepted medical leadership, and the other is the extraordinary cooperation we have

received from the medical profession. Of course we have had individual objectors, but up to the present time every county medical so ciety, save one or two, that has been approached, and this includes more than three-fourths of them, has accepted the program and almost always with enthusiasm

The officers and trustees of the state medical society are so imbued with the value of the present organization that they plan to continue it in a somewhat modified form after the present crisis is over

While this work has been organized to meet an emergency, the procedure that was followed in its formation would have been successful even had the emergency not existed, just as has been that of the New Jersey plan. The officers and trustees of the Medical Society of the State of Pennsylvania were in process of endorsing the original proposal of the State Academy Committee when the call for the emergency committee came to them

The emergency merely made it easier of accomplishment and earlier of realization. In other words, the emergency created the psychological moment for the development of the work. That emergencies do play a very definite part in the development of new lines of procedure in public health is evidenced by the fact that the first state health department ever created was the result of a serious emergency

I have described the Pennsylvania procedure in some detail because I believe it creates a feasible and practicable plan to offset or cure many of the evils that have been referred to above, as well as to provide a very much needed procedure in health protection

The State Academy Committee is not numerically strong enough in any state to make its direct efforts felt in a statewide program. On the other hand, much can be accomplished if the state committees will serve as initiating groups in interesting the state and county medical societies and the various health agencies in a manner similar to that which has been followed in New Jersey and Pennsylvania

Through such procedure we have opportunity to make the Academy a potent force in the field of child health throughout the nation. From the date of its foundation I have been deeply impressed by the possibilities of the Academy in the relatively undeveloped field of preventive pediatrics. The measure of success we will attain depends entirely upon the seriousness and enthusiasm with which the Fellows of the Academy enter the service. It is in our power to lead the way Let us not falter!

#### THE DEVELOPMENTAL HEALTH EXAMINATION

### T WINGATE TODD, FRCS (Eng.) CLEVELAND, OHIO

#### THE NATURE OF A DEVELOPMENTAL HEALTH EXAMINATION

IN PREPARING and interweaving accounts of the developmental growth of children for the White House Conference it was a com paratively easy task to differentiate deviations from satisfactory prog ress so gross that they fall under the caption of ill health for it is within the training and experience of every physician to recognize frankly pathological states which require the application of restora It was however quite another, and indeed a far more difficult problem to determine standards of optimum developmental One clearly could not take the maximum as a criterion for there are aberrancies of excess as well as of deficiency. Progress, moreover, must be balanced. Physical growth may not outstep physi cal maturation. Nor must the physical aspect of developmental growth fall out of line with mental expansion. Mental expansion must be aligned with emotional stability. Experience has great influence in the transformation of capacity into ability. Interests play their part Talent that most unpredictable of all human traits, cuts right across the path of progress and brings its own influence to hear on the de veloping personality. In attempting to outline healthy developmental progress we have then to consider quite other features than those which determine medical health

Medical health is essentially a record of status—developmental health is essentially a record of progress—That is why the serial examination is necessary for the latter determination

Developmental health presupposes absence of any gross deviations from medical health. Hence the developmental health examination may include but does not necessarily imply a medical health examination. In my report on the assessment of physical status\* to the White House Conference it was necessary to build such program of developmental health as we then had upon the routine medical examination. Since that date, the Developmental Health Inquiry of the Associated Foundations in Cleveland has provided the opportunity of outlining in more definite terms those assessments which give us information upon developmental progress. In the Cleveland experimental study these are subdivided into physical orthodonic psychological and so-ciological groupings. Under the physical heading come measures of growth, of maturation, of posture and of nutritional progress. The

Prom the Laboratory of Anatomy Western Reserve University and Associated Poundations.

orthodontic group includes assessments of facial growth, of dental calcification and eruption and of the proper development of nose and nasopharynx. In the psychological group are estimates of muscular power and coordination, of personal social reactions, of reasoning and the handling of factual material, of mechanical intelligence and ability, of self-reliance and emotional stability. The sociological determinations are those of socio-economic stability and advantages, of family integration and group acceptance

Although we are still in the exploratory phase of the subject and many of these measurements are not vet simplified so that they can be effectually and economically put into practice on a large scale, the day is not distant when an adequate developmental health assessment will be devised of so simplified a character that it can be applied in the course of regular practice. And some of the tests at least may even now be utilized with distinct advantage by the pediatrician

### THE CONDUCT OF A DEVELOPMENTAL HEALTH EXAMINATION

A Physical Growth—The significant measurements of physical growth are weight, recumbent length, stature, height of left iliac crest from floor, greatest breadth over iliac crests, bitrochanteric diameter, and length of tibia from articular edge of inner tuberosity to tip of tibial malleolus. Chest measurements and expansion, it must be observed, like vital capacity, fall under the medical examination. The difference between stature and recumbent length gives a measure of posture. The height of iliac crest gives the proportion of leg length to stature. Bi-iliac and bitrochanteric diameters are really measures of maturation. Tibial length is the most easily obtained measure of growth in a limb bone for comparison with stature.

B Physical Maturation —For the estimation of physical maturation roentgenograms are necessary Between birth and fifteen years these should comprise anteroposterior of left hand and wrist, dorsoventral and lateral of left foot and ankle, posteroanterior of left knee All four can with care be taken on two 8 by 10 inch films. Between twelve and fifteen years an anteroposterior roentgenogram of the elbow is of assistance but not really necessary. Between fifteen and twenty years elbow and foot are not required. At that period of adolescence the hand and knee roentgenograms should be taken on a single film and a second film used for shoulder. The details of technique and interpretation are given in my account of roentgenographic appraisement for the White House Conference.

C Orthodontic Appraisement—This is a somewhat specialized assessment the details of which have been fully set forth by my colleague, Dr B H. Broadbent,<sup>2</sup> and its application to the study of nasal passages and adenoid growth will shortly be published by Dr H. C Rosenberger <sup>5</sup>

D Psychological Assessment —The psychological progress is ascer tained by tests appropriate to the age and type of mental expansion on which information is desired. For children of eighteen months or less the Gesell tests are of service. From two to six years the Merrill Palmer tests give a measure of intelligence expressed in performance Motor tests are employed to give a measure of muscular coordination. The Binet test of course measures intelligence expressed vocally, though it assesses only pure reasoning and the handling of factual material. Other tests of useful character are the man drawing test, the Minnesota mechanical abilities tests and paper form board, the Ascendancy-Submission test, the Woodworth Mathews personality rating and the Bernreuter Inventory.

E Sociological Appraisement —The sociologic investigation is still less ready for general application though the Sims socio-economic rating scale gives some measure at least of socio-economic advantages

# THE APPLICATION OF ROUTINE DEVELOPMENTAL HEALTH DETERMINATION TO PEDIATRIC PRACTICE

Accepting the fact that so far, the sociological and orthodontic tests are insufficiently simplified for general use and that psychological assessment demands special training and is therefore as yet very restricted in its applicability to routine practice we still have the measures of physical appraisal which can be utilized at once and interpreted with fair assurance after a little experience. The technique is simple, the cost low and the interpretation not too difficult to be mastered by the busy practitioner.

#### I THE SIGNIFICANCE OF PHYSICAL MLASUREMENTS

The physical measurements selected above will determine the tempo of actual increment in size. They should be compared with the White House Conference tables or those prepared by R. M Wood bury for children under six years<sup>12</sup> and for older white children by Baldwin and Wood<sup>1</sup> or for colored children by Royster and Hulvey. It is true that the Woodbury standards are rather low but we find in practice so many children whose status in physical growth is mediocre though their progress between examinations is satisfactor; that the Woodbury standards are really of great practical advantage for they rarely compel the physician to explain to a parent why the child's progress is not at least average in amount. There are, however, far more important deductions to be drawn from growth progress than the simple satisfaction of parental ambition. In a way increments of weight if paralleled by proportionate increments in stature during the infancy and preschool phases, are measures also of physical matura tion At least the two phases of developmental growth are very closely correlated And the mental development, in the majority of

healthy children, keeps pace with the physical growth. It is our experience that the child who has, by his third birthday, reached the stature and weight of an average five-year-old child as designated on the Woodbury tables, will also have reached approximately the five-year stage in physical maturation and mental progress. It is important to realize that whereas the body takes some eighteen to twenty years to reach adult growth, the brain has practically reached adult size by the sixth birthday. The changes in cerebrum attained after that date seem to be connected with the development of association centers and connections which reduce the depth of the fissural pattern.

The psychologists tell us that the type of mental development changes fundamentally after the age of six years so that, instead of being an elaboration of capacity, it takes the form of a training in ability 4

Children who grow and mature rapidly before the age of five years must not be expected to continue at this tempo during the grade school period. There is, as it were, a plateau of progress which may be attained early or late. Those who reach it early diminish their rate of progress so that by five years there is a greater uniformity of size and maturation than at any earlier period excepting perhaps the first birthday.

After the stage reached between five and six years one may expect, during the grade school period, another phase of increased growth velocity lasting a year or two and expressed in children of good physical constitution rather earlier than in those of less satisfactory developmental health but showing itself in all children under the age of nine years. It is followed by diminished activity of growth during the period of approximately nine to eleven years. After this renewed vigor of growth sets in with the approach of adolescence

Allergic children begin to change their type of growth progress about the age of seven years. Their stature increases out of proportion to their weight and the lean "bean-stalk" type of child begins to show itself. Kretschmer's types indeed are obvious during adolescence but their body form is already demonstrable at a much earlier age.

The early adolescent growth in stature, when expressed on the Baldwin-Wood or Royster-Hulvey standards, is more vigorous in boys than in girls but this is largely a matter of comparison with adult stature. The girl leaches her full height at an earlier age than the boy and therefore the increase in pelvic dimensions is more obtrusive in the girl at this stage. The increase in bitrochanteric diameter is partly due to accumulation of panniculus but is also produced by growth of femoral neck and lateral displacement of great tuberosities of the femora. It occurs rather earlier than the increase in bi-iliac diameter which, in its turn in girls, precedes and accompanies the establishment of the menstrual periods.

Relatively late occurrence of the menarche seems to imply delay in the cessation of stature increase and in union of the copplyses, girls of this type grow taller than those whose menarche supervienes early, largely because growth is possible in them over a longer period of the second decade

Stature increase in boys remains possible through a greater part of the second decade and their adult height is much greater on the aver age than that of girls, a sex difference which is distinctly anthropoid in character since it is far more characteristic of higher primates than of lower primates or non primate mammals

In all interpretations of stature and weight increase the family line characteristics must be reckoned with but nutrition and medical health play a significant rôle as is well seen in Mitchell's studies of Porto Rican children compared with those of the continental United States In general stature and weight increments beyond the average are a rough measure of constitutional health but, also generally speaking they are of less significance in this respect than the roentgenographic appraisement of physical maturation

#### II ROENTGENOGRALHIC APPRAISEMENTS

The roentgenograms suggested earlier in this survey shed a very significant light on developmental growth and health if carefully studied and properly interpreted. They give measures of inneral reserves and therefore of constitutional fitness, of constitutional vulnerability, and of physical maturation. These three features should be considered separately.

The Estimation of Mineral Reserves -Without going into detail on the subject of mineral reserves it may be recalled that Sherman has emphasized the iron rich calcium poor status of the infant? This, however, has no necessary relation to blood calcium studies since blood calcium is merely calcium in transit without indication of its source or destination. Its significance for bone growth neuromusen lar progress and kidney function are, however evident enough chief depots of mobile calcium are the metaphyses of the long bones of the limbs and the bones of the hands and feet Demineralization from whatever cause, as in the ostcoarthritic period in pregnancy in adolescence or in infancy makes its appearance chiefly in these areas In the dimineralization of rickets, epiphyses or carpal bones already ossified may lose their calcium so that they appear as ' ghost centers' in the roentgenogram. We are not concerned in developmental health. with extreme conditions such as this but with the fluctuations observ able in the mineralization of the skeletal depots Epiphysial ossifica tion in infancy and early childhood is but one phase of this minerali zation study Breast fed babies show a slower progress of epiphysial ossification whether or not cod liver oil is administered, than babies

fed upon a non-maternal diet. During the period of adjustment to non-maternal diet the progress in epiphysial ossification is quite slow but a rapid increase in progress is a measure of the completion of adjustment. Babies on cow's milk with cod liver oil show more vigorous progress in the epiphysial ossification schedule between six and twelve months than babies upon other formulae. Boys tend to a slower progress than girls in epiphysial ossification in the latter half of the first year but make up for this tardy progress once they have passed the first birthday. These distinctions still require much further investigation but they are quite evident in a carefully controlled study. Accompanying them can be seen fluctuations in the mineralization of cancellous texture and of compacta though no adequate measures of quantitative determination have yet been devised. The fluctuations are so great that quantitative methods are not necessary for their recognition.

Demineralized infants maintain their functional progress as determined by tests of the Gesell type on motor responses, motor adaptability, and on personal social responses, and even in physical growth for some weeks, though, in a while, they fall behind in the motor and adaptive responses, and, somewhat later, in personal social responses. There is a distinct change in behavior, they become restless, irritable, apprehensive, and querulous. Once these behavior changes have appeared the replenishing of the skeletal depots will not be accompanied at once by a return of serenity in behavior, though the motor responses recover very quickly and often will promptly improve on the administration of an adequate dose of cod liver oil

The demineralized infant is not necessarily sick though disturbances of an exudative or allergic type readily supervene. When that happens the child has passed from the fluctuation of developmental health to the decompensation and failure of reserves culminating in medical ill-health.

The vitamin ration, especially of A, B, and G seems to be closely associated with mineralization and the maintenance of constitutional health in infancy I do not emphasize vitamins C and D, adequate doses of which are usually provided

The rôle of demineralization as expressed in roentgenograms and affecting developmental growth in childhood cannot be touched upon in this survey which is designed merely to open the subject

The Recognition of Constitutional Vulnerability—The determination of damage suffered in constitutional health as the result of an infectious disease or other disturbance of medical health is often a matter of considerable import. The parental measure of a child's actual illness is frequently determined by the resultant disturbance of household routine. But in the absence of evident sequelae we have no adequate measure of the real constitutional setback. The lines of in-

terrupted growth evident on roentgenograms, especially between the third and fourteenth year, emphasized by Park, of Hopkins, give not only an estimate of the severity of the impact upon developmental growth but also of its date. This can be determined easily within a month of the occurrence if the bodily growth increments are known from serial developmental health examinations. Further, the length of time which the transverse line or "scar" remains is an indication of severity, for the longer it takes the bone to remodel its architec tural pattern to climinate the mark the greater the constitutional dis There is some selective activity in these markings on the bones for the lower tibia seems to bear the brunt of dietetic disorders especially those of minor grade, whereas the lower radius, lower femur, and upper tibia are more often scored by the effects of the Much more could be said on this subject if space per exanthemata mitted even though the full story is by no means yet understood

The Assessment of Physical Maturation -It has previously been men tioned that below the age of five years physical measurements give a fair indication of the progress of development or as the theme is better expressed, of progress in maturation. During the grade and high school periods however, physical measurements express growth only, as morease in dimensions. They do not, except in pelvic dimen sions possess any relation to bodily maturation. To determine progr ress in this aspect of developmental growth roentgenograms are necessary During the grade school period extension of ossification into the cartilaginous epiphyses and, during the high school age epiphysial union permit determination of the stage attained in progress toward maturity of the skeleton. Empirically this progress is found to be closely related to general bodily maturation The details of roentgenographic appraisement have been outlined in the White House Conference reports \* 10 Measurement of carpal areas resorted to by many workers is an effort in this direction but unsatisfactory in practice, since no adequate standards of measurement are possible in that portion of the skeleton which is one of the most susceptible to disturbance as a result of ill health or nutritional deficiency Stand ards of progress in maturation, other than those in the White House Conference reports, suffer from lack of precision since they presun pose a range of individual variation. Individual variation does indeed occur when the maturation stage is matched against chronological age but obviously no precise determination can be made upon a scale in volving range any more than upon any other scale the graduations on which are blurred and indefinite. Actual practice in rating of roentgenograms in terms of the details of penetration or of epiphysial union alone can give confidence in this new and exact instrument for measuring physical maturation

#### MEASURES OF SUPERIORITY

It is a simple matter to define a child as tall or heavy for his age, a child who looks old for his years, or a child with a high I Q is the discovery that physical maturation can be exactly determined which has rendered possible the intimate correlation of physical growth and mental expansion A child may be tall and slender and high in Binet rating as most allergic children over seven years actually are, but until the physical maturation progress has been measured we have no adequate conception of the child's actual status. A child may be tall or short for his age but the stage reached in his physical maturation is the really significant factor in determining the more subtle personality traits which interplay with the mental expansion superior type of child, that is a child who has had the advantages of good nurture, adequate socio-economic advantages, and reasonable freedom from disturbances of health and of developmental growth, is tall for his age, of weight a little beyond the average for his height, of physical maturation several months or even two years above the mediocre mean for his years, and of a psychologic rating easily in advance of the average for his age Harmonious superiority implies an approximate equality of advancement in all these features monious superiority or precocity is the result of unequal progress in which one feature far outstrips the others

### RETARDED AND PATHOLOGICAL DEVELOPMENTAL GROWTH

The distinction between retarded and pathological developmental growth is evident even when it cannot be defined. Many girls and still more boys are tardy in entering their adolescent phase but, given time, they will make good the delay the only permanent objective result of which is an increased stature, though there are definite personality modifications and traits which may become permanently impressed upon the individual A pathological interference with adolescent progress is recognizable in character of subcutaneous tissue, in body proportions, in personality traits as well as in the fact, ascertainable at last, that time alone does not suffice to eliminate the handicap For such children treatment is necessary This should to progress be directed toward the reestablishment of metabolic integrity rather than specific medication for growth stimulation. A good example is given by Dr Priscilla White's diabetic children 11 These children retarded, both in physical growth and physical maturation, at once be gan to repair both aspects of the deficiency when they were placed on regular doses of insulin A similar and more generally recognized There are, however many children type is the hypothyroid child subthyroid in diathesis, not retarded enough to merit the definition of hypothyroidism Roentgenographic determination of physical maturation permits the recognition of many lesser degrees of retardation

more temporary in character and usually self rectifying in time, following the exanthemata and other forms of health disturbance fantilism is one of the most intractable of these forms Further con sideration of this aspect of our problem would bring us back into the medical health examination from which we sought to free ourselves in elaborating the theme of the developmental health assessment

- 1 A medical health examination is an assessment of constitutional status a developmental health examination is an assessment of spe cific progress in physical growth and maturation in mental expansion. in emotional stability, and in other aspects of normal healthy childhood
- 2 The conduct of a developmental health examination calls for certain types of measurement which are discussed in some detail in the body of this paper
- 3 Some of these determinations may readily be incorporated in the routine pediatric serial examinations, especially the determinations of physical growth and maturation which properly interpreted throw a very significant light on the progress of growth in childhood
- 4 Of these determinations now available the roentgenographic in vestigation holds the greatest immediate promise
- 5 Greater precision in definition of the superior type of childhood is easily attainable as well as in the segregation of simple and self rectifying types of retardation from the pathological forms which call for medical supervision to restore metabolic integrity
- 6 The developmental health examination opens up a new vista of understanding in the problems and personality of the healthily grow ing child

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# THE MEASUREMENT OF ABERRANT DEVELOPMENTAL GROWTH

I THE MANAGEMENT OF PREADOLESCENT DISTURBANCE

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# THE SUBTHYROID STATE

ANOMALIES of human stature, proportionate growth and maturity level, more especially gigantism and dwarfism, have always fascinated the investigator. Quite recently, with the accumulating knowledge of ductless glandular physiology, disturbed metabolic states have been carefully studied and numerous theories have been advanced to explain the effects of altered metabolism on the progress and endresult of growth and development

Recent experience emphasizes the value of skeletal assessment in the diagnosis and treatment of disorders which involve growth in size or progress toward the mature condition. In our laboratory more than two thousand complete human skeletons and more than thirty-six hundred living individuals below the age of twenty-five, studied roent-graphically, have been used to elaborate standards of progress in maturation. Todd<sup>1 2 3 4</sup> and Stevenson<sup>5</sup> have reported this work. These standards have been utilized in the assessments to follow since they have been worked out and tested more fully than other devices of similar nature. It is possible by this method to estimate the stage of ossific development within a six-month range.

In the study and treatment of aberrant growth it is important to evaluate the anomalous progress toward maturity in the individual Indeed it is in this aspect of developmental growth that the first evidence of a disturbed metabolism is to be found Engelbach and McMahon<sup>6</sup> and Shelton have recently emphasized the retarding effect The current tendency, however, to speak of matuof hypothyroidism ration solely in terms of sexual maturity does not adequately interpret the maturation process Differentiation of features indicates, as clearly as growth in stature, a constant structural change just as significant in its assessment before adolescence as at that precise The W R U standards evaluate these structural phase of life changes throughout childhood and adolescence and are proving valuable in the understanding of all types of failure in the attainment of average developmental progress In the first volume of the White

From the Laborator, of Anatomy and Associated Foundations Western Reserve University

House Conference reports on Growth and Development's some of the conditions which lead to a severe lag in maturation are discussed. Dia betes, for example as well as hypothyroidism and other altered metabolic conditions handicaps the growing child in that it retards his progress toward maturity as well as the attainment of his average family stature.

#### INDIRECT DEVELOPMENTAL GROWTH PROMOTION

In these special cases we have studied both retardation in growth and retardation in development using, for this purpose anthropometric, clinical, developmental, and psychometric technics and bringing each

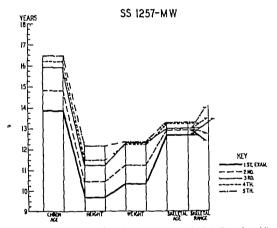


Fig. 1—Chart of growth and maturation progress of 88 1.57 male, white, from the ago of thirteen years ten months to sixteen years five months. Treatment only after third examination at fifteen years eleven months. In skeletal range downwardly directed lines signify retardation upwardly directed lines, progressive maturation.

patient into the laboratory at three month intervals for study while under active treatment. Nearly 200 cases of disturbed development have been recorded and more than 35 cases are being studied and treated at the present time. We have observed that when a nutritional disorder occurs in a growing child, there is a disturbance of developmental growth. In the majority of children this interruption is temporary and the normal progress is again resumed during the period of convolescence. In a few children, following such a disturbance there is no resumption of the original tempo of progress, as though the mechanisms which control growth and development had been definitely mutilated. In these cases a progressive developmental lag be-

comes apparent and adult proportions or complete maturity may never be reached A dwarfism or at best a defective maturation results

In the treatment of these conditions the administration of certain endocrine substances appears to rectify the metabolic functions of the organism and thus promote developmental growth. It is, however, essential to govern the dose by a serial study of developmental growth progress during the treatment. The following cases illustrate how progress under therapy is studied and indicate the promotion of growth at a rate greater than that shown in normal children under our observation or in cases of aberrant growth not under treatment

SS 1257 shows a lag both in statute increment and in maturation, with the progress in statute following growth promotion (Fig 1

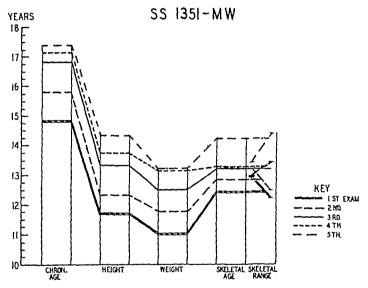


Fig 2—Chart of growth and maturation progress of SS 1351 male, white from the age of fourteen years ten months to seventeen years four months. Treatment only after fourth examination at seventeen years one month. In skeletal range downwardly directed lines signify retardation upwardly directed lines progressive maturation.

Table I) During the first two years while the boy was being studied but not treated, height, weight, and maturation showed much less than the average yearly increments, so that on his sixteenth birthday the boy was retarded the equivalent of four years eight months in height, three years seven months in weight on the Baldwin-Wood standards, and two years nine months in maturation on WRU standards During the next six months Armour's desiccated thyroid (4 grains) and Armour's desiccated anterior pituitary (2 grains) were administered daily by mouth Assessments then registered a height increase equivalent to eleven months on the Baldwin-Wood standards, a stationary weight, and a maturation (or developmental) increment

LOW LAN	CHROY AGE THEOLIT RULDILY WEIGHT ROUNDS) (ALOW) (TODD)  (MALOW) (POUNDS) (MALOWIN (TODD) (TODD)  (MODD) (MODD)	10 mo. 9 days 1385 9 yr 8 mo. 744 10 yr 4 mo. 12 yr 8 mo. 12 yr 5 mo to 1, yr 11 mo. 9 mo. 20 days 1389 10 yr 5 mo. 79 11 yr 3 mo. 12 vr 11 mo. 12 yr 9 mo to 13 yr 0 mo. 11 mo. 9 days 1435 11 yr 3 mo. 884 12 yr 4 mo. 13 yr 0 mo. 1, yr 9 mo to 13 yr 6 mo. 13 mo. 11 days 1446 11 yr 6 mo. 864 12 yr 3 mo. 13 yr 10 mo to 14 yr 0 mo.	3 two years without treatment the facroace are:  Lieght equivalent  Veight equivalent  24 mo	4 mo. Skel ago Tare II	SS 13.01	CHROW AGE LEGGET REMEASEN WEIGHT ROUTINET SKEL AGE SKFL MADE (TODD) (TODD) (TODD) (TODD) (TODD)	10 mo 0 days 1447 11 yr 8 mo, 773 11 yr 0 mo, 12 yr 0 mo 12 yr 3 mo to 12 yr 10 mo 26 days 1484 12 yr 1 mo 824 11 yr 9 mo 12 yr 10 mo 12 yr 0 mo to 13 yr	10 mo. 2 days 1 mo 24 days 4 mo 31 days	
	CHROY AUR	13 yr 10 mc, 9 da 14 yr 9 mc, 26 da 15 yr 11 mc, 9 da 16 yr 2 mc, 13 da	Darling two years w			CHRON AGE	ут 10 mo ут 9 по	16 yr 10 mo. 2 da 17 yr 1 mo 24 da 17 yr 4 mo 31 da	During two years w
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equivalent to three months on the WRU standards. This case is recorded merely as an example of the encouragement of stature increase in retarded adolescence.

SS 1351 is a similar case in which the developmental progress was materially modified following treatment (Fig. 2, Table II)

After two years of simple observation, when this boy was sixteen years ten months of age he was still retarded the equivalent of three years six months in height, four years four months in weight on the Baldwin-Wood standards, and three years seven months in development on the WRU standards Further, the retardation was progressive during the two preceding years when no treatment was given. In

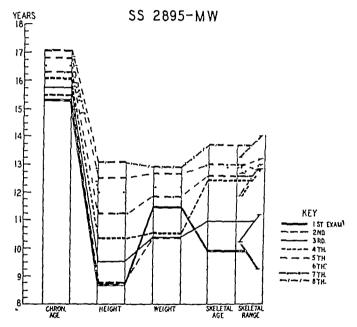


Fig 3—Chart of growth and maturation progress of SS 2895 male white, from the age of fifteen years four months to seventeen years. Treatment throughout entire eight examinations. In skeletal range downwardly directed lines signify retardation upwardly directed lines progressive maturation.

the six months following the institution of treatment the patient grew the equivalent of twelve months in height and nine months in weight He also progressed the equivalent of twelve months in development During this time he received 2 grains of desiccated thyroid and 2 grains of desiccated anterior pituitary for three months, then 4 grains of each for three months This is again an illustration of developmental growth encouragement in retarded adolescence

The detailed relationship of endocrine dosage to progress in developmental growth is presented in the following case (SS 2895), the features of which clearly indicate that a therapeutic program for the promotion of specific effect either of increase in dimensions or of pro-

TABLE III SS 2805

					HEE	HEIGHT		WEI	TUDIAT.						
				HEIGHT	ROUIT	EQUIVALENT	THEIGHT	Equiv	EQUIVALENT	BKEL	AGE		BKEL	BKEL EANGE	
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					W	W00D)	.	(doop)	ω)						
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7	16 1	0 1110	13	1387	10 77	OE 7	10	10	0 mo	12 yr	g mo	11 11	9 дла	to 12 vr	11 mo
10	10 31	3 mo	ô	14 6	1	3 mo	63		10 mo	12 yr	2 mo	11 yr	O mo	to 12 yr	11 шо
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œ	17 71	0 mo	18	1602		1 то	123		11 mo	13 1	9 mo	13 yr	3 mo	to 14 yr	0 то.
	After	twenty	twenty months' treatment the increases are	entment th	e increm	es are									
		Helg	þt	21.		(8½ in.)			Height	Height equivalent		4 yr	5 mo		
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gressive maturation can indeed be worked out. This case particularly illustrates the adjustment of endocrine dosage for the promotion of growth and emphasizes the significance of a serial maturation study (Fig. 3, Table III)

SS 2895 was first studied in this laboratory on May 9, 1931 The boy had been a feeding problem during the first two years of his life, after which time he failed to grow normally At the age of four he had measles, at five chickenpox and at six



Fig 4-A Roentgenogram of left hand SS 2895 before treatment aged fifteen lears four months. B Roentgenogram of left hand SS 2895 after twenty months treatment, aged seventeen years.

mumps Other than this his history was uneventful. His parents are both above the average stature and his family history is negative

In 1926 he had a course of both thyroid and anterior pituitary substance by mouth and became so nervous that after two months treatment was discontinued In 1928 he had another course of thyroid treatment but this was also discontinued because of nervousness and irritability

When first examined in our laboratory he was a fairly well proportioned boy, somewhat lethargic, fifteen years four months thirteen days of age. His voice

had not changed. There was no axillary, puble, or facial hair. The skin and hair were very dry and the subcutaneous tissues were unusually firm. The genitalia were underdeveloped testicles about one and one half centimeters in diameter and penis four centimeters in length. There was also an underdevelopment of the maxillary part of the face with an associated constriction of the posterior massl passages. The basal metabolic rate registered minus 19 per cent and minus 17 per cent on two estimations. Other laboratory chemical tests revealed nothing unusual.

The physical nasessment at this time (Exam. 1, Table III) gave the boy a height age of eight years eight months, weight age of cloven years six months on the Baldwin Wood standards, and a skeletal age of nine years eleven months on our

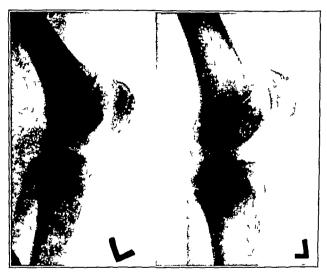


Fig. 5—A. Roentgenogram of left knee before treatment 85 2895 fifteen years four months. B Roentgenogram of left knee after treatment 85 2395 seventeen years. Note transformation of cauliflower-like mineralization of patella into normal casification after twenty months.

standards. There was a marked osteochondritis of the patella and of the navicular bone of the foot.

At this time Armour s thyroid gland tablets were prescribed 2 grains each day not anterior lobe pituitary tablets, 4 grains a day. Two weeks later the dose was increased to thyroid 4 grains, and pituitary, 6 grains. This dosage produced hendache sleeplessness and a mild glycosuria. It was therefore reduced to 2 grains of thyroid and 6 grains of pituitary a day. Two weeks later the glycosuria and other disturbances had disappeared and the 4 grain thyroid, 6-grain pituitary dosage was resumed. No further disturbances occurred.

After two months of this regime (Exam. 2, Table III) the boy had lost ten pounds in weight and had not increased in height. The skin was then not so dry and the subcutaneous tissues had lost their unlicality firmness.

# A SURVEY OF ONE HUNDRED CASES OF CONGENITAL SYPHILIS TREATED WITH STOVARSOL (ACETARSONE)

# HAROLD A ROSENBAUM, M D CHICAGO, ILL

DURING the past few years the use of stovarsol (acetarsone\*) in the treatment of syphilis, especially congenital syphilis, has been detailed by a number of writers 18. A survey of 100 cases of congenital syphilis thus treated seems desirable at this time. Our treatment was patterned after that of Bratusch-Mairain, which is as follows 0.005 grams of the drug per kilo body weight is given for one week, followed by 0.010 grams per kilo daily for one week, 0.015 grams per kilo daily for one week, and 0.020 grams per kilo daily for six weeks. This is followed by a rest period of one month and the course repeated until the serologic tests are entirely negative, and three courses are given thereafter. A rest period of six months is then given and then one more course of treatment.

The serologic tests used by us consist of a Wassermann reaction, using acetone insoluble and cholesterinized antigens, and a Kahn test In our series there were 46 cases in which treatment was begun in the first year, and 54 cases in which treatment was started in children over one year of age. This division is made because treatment in the young infant results, as a rule, in prompter clinical and serologic improvement.

# TOXIC REACTIONS

Toxic reactions occurred three times in the older group and twice in the younger group. In this latter group there were 3 patients who developed toxic reactions in whom it was doubtful that the symptoms were due to stovarsol. Thus the percentage for the series showing toxic reactions was 5 and possibly 8. Most of these reactions were very mild, consisting of an erythema and in a few cases a rise of temperature. Diarrhea did not appear as a toxic symptom in our series of cases, when it was present it was due to some other cause. In one patient a girl of ten and a half years, there was a marked erythema when given sulpharsphenamine, but no reaction to stovarsol

Three patients in the older group showed toxic reactions. One was a boy, three years five months old, who developed a generalized macular rash twelve days after beginning treatment. Stovarsol was dis-

From the syphilis clinic of the Childrens Memorial Hospital Chicago Ill
\*Acetarone is the name used in New and Non official Remedies of the American
Medical Association and is the same chemically as stovarsol and spirocid The drug
stovarsol used in this series was kindly furnished to us by Merck & Co

continued for two weeks and then resumed without reaction ond patient, a girl five years mine months old, developed an erythema on the dorsal surfaces of the upper and lower extremities a few days after treatment was begun. No treatment was given for a week rash disappeared and treatment with stovarsol was begun again, this time without reaction. The third patient, a white girl of seven years. had an interstitial keratitis. After three weeks of treatment she developed an erythema over the upper chest and the dorsal surfaces of the upper and lower extremities together with fever up to 1025° F Stovarsol was discontinued and begun in ten days when a similar cutaneous and febrile reaction occurred Stovarsol was not attempted again During this time, however, the keratitis made very rapid im provement the right eye almost clearing, and the left cornea remain ing only slightly hazy

Two patients in the group treated during the first year showed toxic reactions. One was a white girl of nine months who on the day after the beginning of stovarsol treatment developed a temperature of There were no associated findings and the temperature re turned to normal the next day On the day following the day of nor mal temperature through a misunderstanding the mother gave an other dose of stovarsol and this time the temperature rose to 103° F Gray powder was then given for two weeks after which stovarsol was again given and this time without reaction. The other patient in this group was a white boy two months old who was given 0.05 gm of stovarsol for two days. He developed a temperature of 104° F and had a convulsion as reported by the neighborhood physician who cared for him and subsequently treated the syphilitic condition

In three patients of this younger group it was doubtful that the pa tient reacted adversely to stovarsol. The first patient was a congenital syphilitic admitted to the hospital with bronchopneumonia, bilateral purulent of itis media large spleen and liver and bone syphilis days after treatment with 006 gm. of stovarsol daily he died second was a white infant of three months with bronchopneumonia visceral and mucous membrane syphilis who was given 006 gm of stoyarsol daily for three days Antisyphilitic medication was discon tinued because he seemed very sick. He died three days later was no evidence that death was connected with stovarsol patient in whom stovarsol had a doubtful toxic effect was a girl of six weeks with a bloody discharge dripping from her nose. The head was held retracted There were scaling and infiltration of the inter evebrow region a maculopapular rash cylindrical-shaped chest and abdomen with marked retraction of the lower chest with each inspira tion, the liver was firm and on a level with the umbilious tient died after 0.06 gm, of stovarsol had been given for two days

# SEROLOGIC REACTIONS

Serologic response was very satisfactory For purposes of comparison to the stovarsol treatment, we treated a group of 29 infants, beginning in the first year and continuing for one year, by the older methods of treatment, that is, with injections of mercury, bismuth, and the arsenicals, and gray powder by mouth The same was done with a group of 48 patients in whom treatment was started after the first year of age and continued for one year In the younger age group of 46 cases there were 35 treated with stovarsol for one year Of this group 3, or 8 per cent, were positive at the end of one year of treatment One in this group of 35 had negative serologic tests when first seen at seven weeks. Treatment was given to the child, however, because the mother had syphilis with very little prenatal treatment, and the child was pale, had snuffles and a palpable spleen This leaves 3 out of 34 cases or about 9 per cent still positive. In 20 of these cases in which treatment was begun in the first year, reversal followed the first course of treatment, in 7 it followed the second course, and in 4 it followed the third course

In this age group of the 29 cases previously mentioned, treated by the older methods of treatment, 18 or 62 per cent were positive after one year of treatment. These must not be considered Wassermannfast cases, as many of them became negative in the second, third, or fourth years of treatment, and the same applies in the older age groups

In the older age group of our series of 54 cases treated with stovarsol, 23 were not treated for as long as a year, leaving 31 cases. Three of the 31 cases, however, had negative serologic tests on the blood when treatment was begun, one of these three had a positive spinal fluid. Of the remaining 28 cases treated for one year, 16, or about 57 per cent, showed reversal following treatment, as compared to 80 per cent positive, or about 20 per cent, which showed reversal at the end of one year of a group of 48 cases treated by the older methods. As stated, these must not be considered Wassermann-fast, as many later became negative. In this older group a few had some little treatment before stovarsol was begun

In this group of 28 older children treated with stovarsol, 5 patients became negative following the first course, 5 following the second, and 6 following the third course By reversal we mean not only an entirely negative Wassermann test but also a negative Kahn test Frequently the Kahn test was persistently one- or two-plus when the Wassermann was negative

The patient with the positive spinal fluid and the negative blood tests is of sufficient interest to be detailed here RT, at about three and a half years of age, developed attacks of unconsciousness lasting fifteen to twenty minutes. These were two to three weeks apart. He had been treated in a neuropsychiatric clinic with

calcium luctate gr x, t.i.d. which seemed to free him of these convulsive attacks. However, he began to have severe spells of night erving which could not be explained by the parents. They were so prolonged that on several occasions the neighbors threatened to call the police. He was so pritable, quarrelsome and constantly on the go that he could hardly be managed at the near by settlement house. He behaved in a similar monner at the dispensary. After several months it was learned that the parents had syphilis and were under treatment. The child was sent to us for a consideration of syphilis. We found a boy of four years and four months with a squarish head with marked veins and prominent frontal bosses and suggestions of rhagades about the mouth. As stated the blood Wassermann and Kahn tests were negative but the spinal fluid Wassermann was acctone insoluble antigen oneplus, cholesterinized antigen two plus. The Lange colloidal gold test and the Pandy test were negative. The cell count was 15 mostly lymphocytes

Treatment with stovarsol was begun and in a month the mother unsolicited reported that he was sleeping better and that he was much more easily managed. At the dispensary the child was tractable and quiet. Because we were dealing with cerebrospinal syphills our dosage was increased to one fourth more than our usual full dose. After six months of treatment the spinal fluid was entirely negative and now after a year his general condition and behavior are excellent

In one patient in the younger group treatment was begun at nine months of age The general improvement was excellent but the Wassermann seems fast. That Wassermann fast cases occur also with the older type of treatment and even when treatment is begun very early is shown in the following case

A boy three weeks old had mercury injections with alternate courses of sulphar aphenamine in full doses and gray powder by mouth for fourteen months. At the end of this time he had four plus Wassermann and Kahn tests. The family was dissatisfied because the serologic tests were not negative and took the child to a clinic where bismuth therapy was given. After a year they returned because the serologie tests were still four plus.

Improvement in the general condition of these patients is the rule Their color improves rapidly and many gain markedly in weight. For example one child of two and one-half years gained 7 pounds in eight months, another, a girl of seven years three months who weighed 35 pounds when treatment was begun, gained 7 pounds in four months without change in regime Condylomata disappeared in from one to two weeks Interstitial keratitis responded more rapidly than usual, eg, the first case detailed in the older children with toxic symptoms Another was able to read two lines farther down on the chart for test ing vision after four weeks of treatment. James' reports 7 cases of interstitial keratitis in which very satisfactory improvement was made with stovarsol Hydrarthrosis and bone lesions responded very well The improvement in one case of cerebrospinal syphilis is recorded

#### SITMMARY

One hundred cases of congenital syphilis treated with stovarsol are surveyed Serologic and clinical improvement was very good

reactions to the drug occurred in from 5 to perhaps 8 per cent of the cases, and they were usually mild in character Serologic reversal was very much better with stovarsol than with the older methods of treatment

## CONCLUSION

Stovarsol by mouth in rational conservative dosage, such as that of Bratusch-Marrain, is a valuable drug in the treatment of congenital syphilis

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#### CONGENITAL OSTEOSCLEROSIS

GEO E ROBERTSON, M.D., BROOKLAN, NEW YORK

CONSIDERABLE interest has been aroused in the study of bone changes in anemia as a result of the reports of Cooley, Witwer and Liee 1 Vogt and Diamond and others. In the condition described by these authors, there is a widespread bone change which apparently develops secondarily to a peculiar type of anemia. In the condition to be reported in this paper, an anemia is found associated with bone changes, but the relationship of cause and effect seems to be altered

Albers-Schönberg, whose name usually identifies this disease first called attention to the condition in 1904. Since that time, less than 40 cases have been described under a variety of different names. These include marble bones osteosclerosis congenita osteosclerosis fragilis generalisata, osteosclerotic anemia osteosclerosis with various types of leucema and osteopetrosis. Karshner's has reviewed the literature to 1926 and gives abstracts of all cases reported together with a description of the clinical course and the roentgenologic findings. Primes has, more recently, described the progress of the disease as revealed by the roentgenogram in a series of cases which he has been able to follow over a period of twenty-one months.

The characteristic finding in congenital osteosclerosis is the roent genologic demonstration of an overgrowth of the cortical portion of bone at the expense of the medullary cavity. The overgrowth is en turely endostal and no enlargement of the bone occurs except in con nection with the ends of the long bones where clubbing and deform ity is frequently found. All bones of the skeleton are involved but the degree of involvement may vary in different parts. When the osteosclerosis is fully developed the roentgenogram reveals a dense, homogenous bone shadow in which no normal markings or evidence of normal hone structure can be discerned. This appearance is usu ally most evident in the bodies of the vertebrae the central portions of the pelvis, the base of the skull and the ends of the long bones The roentgenogram usually demonstrates structions in the flat bones nerallel to the horders and transverse structions or bands of lessened density in the sclerosed areas of the long bones. In these bands, bone trabeculations can be seen, a fact which is taken to indicate the occurrence of remissions in the course of the disease

From the Department of Pediatrics The Long Island College of Medicino and The Long Island College Hospital. Read before the Brooklyn Pediatric Society Jan. 25 1923

The secondary manifestations of the disorder are the most important. These include retarded growth, anemia with enlargement of the liver, spleen and lymph glands, hydrocephalus, optic atrophy, pathologic fractures, imperfect dentition and mandibular suppuration. The secondary manifestations are not constantly present but vary with the degree of involvement of the bones. The severe forms usually occur in childhood, usually show a fairly complete development of secondary manifestations and are progressively fatal.

The disease exhibits a distinct familial tendency in its incidence Multiple cases in a single family have been reported by several au thors. In four instances the condition has occurred in one of the parents as well as in the child. O 7 lo but in most instances the parents have been normal 8 0 10 11

It appears as though the disease has its beginning in fetal life Pririe reports a roentgenogiam showing a fetus in utero which, from the density of the vertebrae, suggested a case of marble bones. He reports this child again, at the age of five years, as a definite case of marble bone disease. Three neciopsies have been recorded in which osteosclerosis has been found in infants dying soon after birth <sup>12</sup> <sup>18</sup> <sup>14</sup> The condition is more frequently met with during childhood but has been recorded as late as fifty-eight years of age <sup>16</sup>

The cause of the disorder is not known Heredity, congenital osteogenetic defect, syphilis, chronic infection, endocrine disturbance involving any or all of the following glands, hypophysis, parathyroids, thyroid and thymus, and avitaminosis, all have been indicted by different authors as the cause While the occurrence of the condition in association with endocrine disorders is frequent, heredity or a congenital defect in osteogenesis seems to be a logical interpretation of the etiology

The pathogenesis of the condition is not understood. It would seem as though there must be an alteration in the calcium and phosphorus metabolism but, save for a few determinations, the blood chemical values for calcium and phosphorus have been found to be normal Determinations of calcium balance have revealed an increased urmary excretion of calcium but no definite evidence of increased retention <sup>17</sup>. The calcium content of the pathologic bone has been found to fall within normal limits. Kooylow and Runowa<sup>18</sup> have shown a marked decrease in the phosphorus and an increase in the magnesium content of the pathologic bone.

As a part of the general retardation of growth, the development of centers of ossification is usually delayed and ossification of the cranial sutures is late. The interference with growth has been explained on the basis of dysfunction of the hypophysis. The osteosclerotic process in the skull produces marked changes in and about

the sella turcica Frequently the sella is narrowed and a characteristic finding is thickening and clubbing of the posterior clinoid process At necropsy the hypophysis is usually small

The type of anemia found in these cases is not specific. It is brought about in the replacement of hone marrow by cortical overgrowth and does not differ from anemia produced by the replacement of bone marrow by tumor metastases or leucemic infiltrations. This type of anemia is usually termed osteosclerotic or myelophthisic anemia 18, 20 The characteristics of this anemia are as follows. There is a marked reduction in both the crythrocyte count and the hemoglobin content. making the color index slightly under 1 Anisocytosis and poikilocytosis are present and immature, nucleated red cells are usually found Myelocytes and myeloblasts are present in the blood smear. The in crease in the mycloid cells may bring about a lencocytosis though a leucopenia is not unusual. As a terminal manifestation, there may be a decrease in blood platelets and other characteristics of aplastic The severity of the anemia is dependent on the amount of bone marrow destroyed by cortical overgrowth but is influenced by the regenerative power of the remaining marrow and the degree of extramedullary hematopoiesis which may occur 21

Enlargement of the liver, spleen and lymph glands is a common finding associated with anemia. Pathologically these organs show a marked myeloid reaction with extramedullary hematopoiesis which might be considered a reversion to the embryonic type of blood for mation. In one necropsy foci of hematopoiesis were found in the kidney. The degree of metaplasia of the myelogenous elements may result in the production of a blood picture which resembles that of lengenna.

Bone changes occurring in the skull, while not limited to the base, are most marked in this area. The most remarkable point in connec tion with the sclerosis of the base of the skull is the narrowing of the foramina which is produced. Hydrocephalus has been noted, particu larly in the younger patients and has been explained as arising from the circulatory disturbances produced by the narrowed foramina more important result of the changes at the bast of the skull is the production of optic atrophy Like hydrocephalus, optic atrophy is noted particularly in the younger cases, but the two phenomena are not always found associated Optic atrophy is probably produced by pressure on the nerve as it passes through the narrowed optic fora Epistaxis may be a manifestation of pressure on the ophthalmic men vein. Distortion of the orbital cavity may cause a slight exophthal mos In many cases a nystagmus has been observed and interpreted as a result of sclerosis of the bony labyrinth.

The occurrence of pathologic fractures has often made possible the diagnosis of mild forms of the disease. The increased fragility which permits these fractures to occur belies the implied hardness in the descriptive term, "marble bones" Pririe feels that the term, "chalky bones," better describes the condition. Karshner prefers the term, "osteopetrosis" Pathologic fractures have been found as early as four months of age, though they are more usual in later childhood and in adult life. A peculiarity of these fractures is that they occur at right angles to the shaft of the long bones, a feature attributed by some authors to decreased elasticity and, by others, to abnormal fragility at the points of the transverse bands of lessened density which the roentgenogram reveals

As a part of the general disturbance, dentition is usually delayed and the teeth are imperfect. Dental caries is very common. A marked tendency toward the development of suppuration of the lower jaw has been noted. This process is probably a consequence of insufficient blood supply occasioned by pressure on the alveolar artery as it traverses its bony canal in the mandible.

The course of the disease is essentially chronic. The osteosclerotic process, per se, is not incompatible with life. The secondary manifestations constitute the serious menace to life. The severe forms in childhood are invariably fatal, death being due, early, to severe anemia and asthenia, while, later, suppuration of the lower jaw is usually linked with a fatal outcome. Goodall's patient died at ten weeks with a hemoglobin of 22 per cent, while the earliest death in a case in which suppuration of the jaw was present, occurred at five months. If the disease is not severe enough to produce serious secondary manifestations, the process may become arrested and the outlook, then, is fairly good. There is no known method of eradicating or arresting the osteosclerotic process.

There is no treatment which seems to have any effect on the disease. Treatment with a diet in which calcium is restricted seems to be of no value. The use of ammonium chloride has produced no tangible results. Zadek calls attention to the fact that irradiation of the long bones or spleen is contraindicated. Splenectomy, a procedure which also would seem to be contraindicated, has been performed without benefit. Pehu has advised a partial removal of the parathyroid glands. The little we can do is to endeavor to pievent the occurrence of fractures by guarding against trauma, to enforce strict dental hygiene to avoid dental infections, to supply iron salts and blood building preparations to combat the anemia and to avoid those substances which promote calcification.

The following patient presents the typical picture of congenital osteosclerosis

#### CASE REPORT

N Z., female Italian aged ten months, was admitted to the hospital on Dec. 24 1931, with the complaint of failure to gain. Both grandparents on either side had died from unknown causes at advanced age. One of the father a brothers had died at five years of age from a disease which had been present from hirthy producing deformities of the legs. An accurate history of this illness could not be obtained. The father and mother of the patient were normal. There were no other children and there had been no other pregnancies. In 1923, the father had received treatment for a change. His blood Wassermann test had been negative, at that time, and on repeated examinations in intervening years.



Fig. 1 .- Facios at 10 months of age.

The child had been born at full term by a difficult forceps delivery after a protracted labor. The birth weight was 6% pounds. The newborn period was normal.

The infant had been breast fed for one month and was then changed to a modified cows milk formula. From birth until three months of age, the child had been given 5 drops of riosterol three times a day. From three months of age until the time of admission to the hospital, she had received 3 teaspoonfuls of 10-D cod liver oil daily

The child was able to sit alone at seven months. The first tooth appeared at eight months

The parents had always noticed that the child was rather pale and that the pallor was increasing. She had never taken her formula well and had gained weight very slowly. About two months before admission, the infant had bled, a little from the nose over a period of four days. One week later this was repeated for a day. There had been no bleeding since that time. There had been no rounting or other gastrointestinal symptoms

Physical Examination The patient was a poorly nourished, poorly developed, fe male infant weighing 15 pounds and 2 ounces. The facies were rather peculiar, there was a marked pallor with a slight yellowish tinge, the expression was apathetic and rather mask like, the forehead was broad and high and there were prominent frontal eminences, the cutaneous veins were dilated, the eyes were widely separated and prominent but normally shaped, the bridge of the nose was very slightly de pressed, the malar eminences were not prominent, the chin was small and receding, the entire face seemed a little puffy and prematurely aged

The head measured 45 cm in its largest circumference. There was a peculiar stony consistency to the cranial bones. There were prominent bosses over the parietal bones with a depression along the sagittal suture. The anterior fontanelle

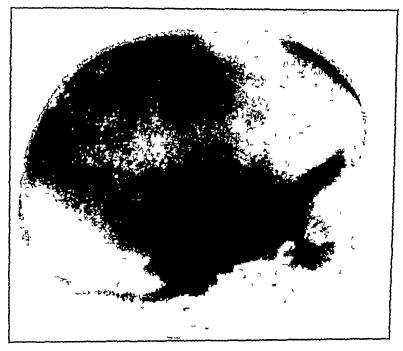


Fig 2—Roentgenogram of the skull showing increased density of all cranial bones especially marked at the base. The posterior clinoid process is clubbed

was open about 2 cm and was slightly depressed. The bonv edges of the fon tanelle were firm and slightly everted

There was a constant, fine, rapid avstagmus Light perception was apparently present but no other evidence of vision could be elicited Examination of the fundishowed a bilateral optic atrophy

There was one tooth present This had a white, chalky appearance

The abdomen was full, particularly in the left upper portion. The spleen tip was palpable at the level of the iliac crest, the organ being very firm in consistency and smooth. The liver edge was at the costal margin. The inguinal lymph nodes were slightly enlarged.

There was no deformity of the extremities and there was no disproportion of these parts to the rest of the body

#### Laboratory Findings

Red blood cells	3,480 000	Blood platelets	240,000
White blood cells	7,100	Bleeding time	4 minutes
Hemoglobin	60%	Clotting time	6 minutes
Polymorphonuclears	23%	Normoblasts	8 per 100 WBC.
Lymphocytes	40%	Reticulocytes	9%
Mononneleura	15%		
Lymphoblasts	3%		
Myelocytes	7%		
Mycloblasts	3%		

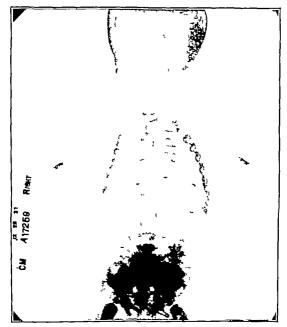


Fig. 3—All bones of the skeleton showed marked increase in density. In the upper extremity this is most marked at the ends of the bones.

Anisocytosis polkilocytosis and polychromatophilia present

Fragility test—hemolysis began at 0.52% and was complete at 0.40% (control -0.44 to 0.32%)

Blood Chemistry—N.P.N.—334 Sugar—878, Serum Chlorides—596 Calcium—10.1 Phosphorus—4.0 Icterus Index—11 Seroprotein—57 Albumin—4.1 Globulin—1.6.

Urmalysis including urobilinogen test was negative

Blood Wassermann tests on the patient and both parents were negative

The diagnosis was made by roentgenologic examination. The following report was made by Dr A. L Bell

"The skull appears to be of moderate size. The suture lines are normally out hined. All of the bones of the vault and also those of the base are slightly thick ened and unusually dense, with a rather marked obliteration of the normal bony architecture and bony trabeculations. The sella turcica is faintly demonstrated and appears to be moderate in size and normal in outline. There is marked in creased calcification noted in the clinoid processes which show obliterated bone texture.

"The remainder of the skeleton, including the vertebrae, thorax, upper and lower extremities, and pelvis, all show similar changes. These changes are also noted in the epiphyses. In the long bones, especially in the upper extremities,

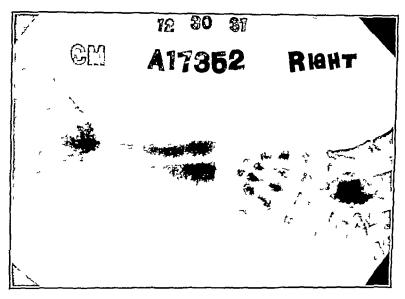


Fig 4—In the bones of the forearm transverse striations can be seen near the epiphyses. The bones of the hand show hour glass areas of increased density

the mid portions of the shaft show some normal bone trabeculations but in the epiphyseal portions of the shafts on either side there is marked obliteration of the normal bone texture and marked calcification. This is demonstrated to a lesser extent in the bones of the hand."

"Conclusion 'Marble Bones'"

The child remained in the hospital for twenty four days. Two small trans fusions were given. Ammonium chloride was given in doses of 5 grams per day. An attempt was made to limit the calcium intake but considerable difficulty was experienced with the administration of solid foods, making it impossible to eliminate milk from the diet. Repeated blood studies showed immature cells in the normo blastic, myeloblastic and lymphoblastic series, with a total white count gradually rising from 7,000 to 15,000. There was a noticeable increase in the size of the spleen and the liver became palpable to 2 cm below the costal margin. She was discharged from the hospital with a hemoglobin of 70 per cent.

One month later the child was readmitted to the hospital with a hemoglobin reading of 55 per cent red cell count of 3,160 000 and white cell count of 20,500 There had been little change otherwise in the general condition.

During the year following this the child was seen infrequently. There was a progressive enlargement of the liver and spicen a gradual increase in the anemia, poor weight gain retarded growth and frequent attacks of epistaxis.

The last examination was made at .. 3 months. About a week prior to this, the child had had a sovere epistaxis

The head measured 40.4 cm in circumference. The anterior fontanelle was closed and there was a bony bulge in this region. There was a slight exophthalmor, Seven teeth were present all presenting a flat chalky white appearance. The alveolar margins were tremendously thickened so that the arch of the palate was represented by a groove about 1... cm in width and depth. The abdomen measured 55 cm, in circumference. The liver edge was 35 cm, below the costal margin. The speen filled the entire left half of the abdomen the tip being in the pelvis and the body of the organ producing a bulge in the flank. Epiphyses were slightly enlarged. There were two small purpuric spots on the right leg

The hemoglobin was 3, per ecut the red cell count 1880,000, the white cell count, 49,800, the platelets, 110 000 Bleeding and clotting times were normal. The stained smear presented a most bizarre picture. The differential count was polymorphonuclears, 29 per cent myelocytes 15 per cent myeloblasts 10 per cent lymphocytes, 32 per cent lymphollasts 8 per cent monocytes 5 per cent, cosinophiles, 1 per cent nucleated red cells, 14 per 100 WBC reticulocytes 15 per cent. Fragility test—hemolysis began at 0.48 per cent and was complete at 0.32 per cent (control 0.44 per cent to 0.28 per cent). The blood calcium was 0.0 mg per 100 c.c. and the blood phosphorus was 2.0 mg per 100 c.c. The icterus index was 8

Since this examination the chief feature of the child's course has been repeated attacks of severe epistaxis, occurring at weekly intervals but without other purpuric manifestations. In spite of the marked anemia the child recently survived a sovere upper respiratory infection.

#### COMMENT

The striking feature in the history of this case is the large amount of vitamin D which the child received. The idea that osteosclerosis may represent the extreme in the healing of a rachitic process has been advanced but is generally discounted since rachitic changes have not been demonstrated in these cases. The administration of vitamin D may accelerate the progress of the condition. In this counection the blood chemistry is of interest. Both determinations of phosphorus have given low values the second determination after thirteen months without added vitamin D in the diet giving a value suggestive of active rickets. It is difficult to reconcile this last determination with an increased rate of calcium deposition. Though roentgenologic evidence is lacking it may be that the disease process is in a stage of remission.

The entire subject of the relationship between bone changes and blood changes is probably much more complex than this presentation would seem to indicate. The possibilities that bone changes in this condition are secondary to or simultaneous with bone marrow changes

was assumed that those animals which produced a milk of low curd ten sion in the second month of lactation would continue to do so throughout the major part of the remainder of their lactation period. This assumption proved to be erroneous, for it was found that some of those animals, chosen early in March as producers of soft curd milk had changed by April 1 to producers of milk of medium hard curd, neces sitating their being discarded. Moreover, throughout the period from April 1 to October it was necessary to replace certain animals with others because of the change in the curd tension of their milk. It was planned to furnish milk of a curd tension below 30 grams, but in reality during certain short periods the tension increased to 30 to 35 grams or even higher on occasion before the individual cow responsible for the increase could be replaced by another of lower tension

The cows chosen were healthy, nomenactors to tuberculin and abortion tests, and were included in the two-time string. It was planned to furnish the mixed milk of not less than three animals. In all, nine animals were used—6 Holstein-Friesian and 3 Avrshires. To insure a milk of good quality both from the standpoint of bacterial content and of flavor, not only were the utmost precautions taken from the sanitary standpoint but also feed was withheld from the animals during the five hour period previous to milking. That the count for the total period showed a maximum of 11,000 per c.c., a minimum of 1,000, and an average of 5,100, and that the milk was of excellent flavor at all times, bespeaks the care of handling and producing

The milking was done in mid afternoon, the supply was immediately cooled, bottled packed in iced containers, and shipped immediately to its destination in San Francisco. One man was responsible for this phase of the study throughout the period. Samples were analyzed chemically daily, were scored for flavor daily, and were examined for bacterial count at least weekly.

Table I summarizes by months the results of the duly chemical analyses. Fat percentages were obtained by the Babcock method, and total solids gravimetrically using the Mojonnier machine, the solids not fat being determined by difference Casein and total protein were determined using the formaldehyde titration method. It was felt that this method was sufficiently accurate for the routine daily analyses, especially where comparative values were desired. In the determination of ash the standard procedure was employed.

The sele purpose of determining the coagulability by rennin and the  $P_{\rm H}$  value of the milk was to indicate that it was normal milk. Physiological disturbances in the cow have been found to be reflected in these values as definitely as such indices as changes in body temperature, for instance. The rennin congulation values were determined using a 2 per cent concentration of rennin and temperature of 39.5° C. The  $P_{\rm H}$  values were determined electrometrically using the Type K. Leeds and Northrop Potentiometer and Bailey type hydrogen electrode. The rennin coagulation and  $P_{\rm H}$  values elevily indicate that the milks used throughout the study were normal for cow's milk

The curd tension values were determined using a modification of the method described by Hill<sup>3</sup>. The curd knives were exactly 2 inches in diameter, a Chatillon's improved spring balance was used to measure the tension, but instead of using the

Monthly Summar of the Analisms of Daily Samples of Lon Cord Tension Milk!

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A Ashenfelder Kit and 1860 Calories per pound solids not fat (III 'tgr Kxp. Sta. Bull. No 108 1918) No. 8, p. 761, 1811 Table II. 'Analyses made by N P Tarassic and Mas M. Calculated on basis of 4,220 Calculated per pound tachienberg and Voris. Jour Agr Research 48:

mayonnaise jar, special jars 23/16 inches in diameter having flat bottom and straight sides were procured Cut off rain gauges were found very satisfactory For the coagulant, rennet extract was found not only to yield results very similar in value to the persin calcium chloride mixture described by Hill, but also gave less trouble in securing duplicate readings and less ' piling'' with certain milks Fresh rennet was kindly furnished monthly by Chr Hansen's Laboratory, Inc. When kept cold these samples were found to decrease only very slightly in strength during the One c.c of rennet extract was quickly added and stirred into 100 c.c month Clotting in the case of unheated milk is almost instantaneous 37.5° C is not only closer to the optimum temperature for rennin congulation, but also more nearly approximates body temperature than 35° C, it seemed desirable to employ the former temperature during the remain action This was followed during the month of April However, because the curd test at the higher tempera ture is a few grams higher than at the lower, in order that these tests should be com parable with those already reported, it was decided to employ the lower temperature throughout the remainder of the study

TABLE II

CURD TENSIONS OF VARIOUS FORMULAS

RAW LOW TEN				CURD TENSION	
SION MILK OZ	karo TBSP	WATER OZ	RAW GRAMS	BOILED 3 GRAMS	BOILED 10
14 15	67	-	27 30 32	13 13	13 12
16 16 18	2 3 3	-	19 28	10 3 13	6 1 7
20	3		36	11	11
14 15 16 18 20	2 2 2 3 3	10 9 8 6 5	8 10 8 14 17	7 6 9 7 11	7 6 10 7 9
RAW CERTI FIED MILK	k 1ro	WATER	PAW	BOILED 3'	BOILED 10'
14 15	3 5 6 6	-	38 40	5 9	3 7 9
16 16	2 3	-	58 46	9 7	4
18 20	3		35 45	11 10	10 10
14 15 16 18 20	2 2 2 2 1 3	10 9 3 6 5	16 17 23 27 31	7 6 8 10 11	6 9 9 10 9
EV \PORATED	KARO	WATER	RAW.	BOILED 3	
Blank 15 15	- 2 2	- 9	3 3	3 3	
RAW MARKET	KARO	WATER	RAW	BOILED 3'	
Blank 15 15 15	- 2 2	9 analysis F	87 73 28 28	14 9 7 F 10 32%	

<sup>\*</sup>Reconstituted 1.1 Final analysis Fat 3.0% S.N. F. 10.329 †Random sample Fat 4.4% S.N. F. 8.97%

In making the tests reported in Table II, in which the effects of dilution, ad dition of syrup and henting were studied it was necessary to add calcium chloride to obtain rapid clotting especially in the heated samples. Hence, the unmodified IIIII test, excepting the jars was employed throughout that series of observations.

In making the readings the balance was mounted in a vertical position over a morable platform. The jar with its contents was placed on the platform, the bal nace was attached to the knife and the platform was slowly and carefully lowered until the knife was drawn through the curd.

That there were considerable fluctuations in the composition of the milk from time to time is indicated by the wide differences in maxima and minima (Table I). As stated before precautions were taken to guard against this occurrence especially in connection with the selection of animals their care feed, and the handling of the milk. Frequent tests of the milk from the individual cows, however showed definite variations, making it necessary to replace certain animals with others or in making up the supply of nuxed milk to use only a minimum quantity of the milk of that animal yielding milk of highest curd ten sion. The maximum values therefore, appeared as seldom as possible throughout the period, usually not over two or three times in any one month. Changes in climatic conditions unquestionably played an important rôle in inducing variation in the percentage composition of the milk.

While as yet no well-defined quantitative relationship can be established between the curd tension and the percentage composition of the milk, yet the fluctuation in the latter (Table I) is usually reflected in the fluctuation of curd tension. The term "soft curd" is as yet not uniformly defined, but it is felt that the milk used throughout this study with the exception of those few samples already referred to is representative of soft curd "milk.

Little comment needs to be made in connection with the fat content of the milks, but inspection of Table I reveals that the average per centages of solids not fat are considerably below what are considered normal for the breed for the corresponding fat content. This is quite apparent when one compares the average values for each month with the analyses reported by Kahlenberg and Voris on the milk from 12 Hol stein Friesian cows over the entire lactation period. It may also be observed that the concentration of protein in this low-curd tension milk is low when compared with that of the mixed herd milk of similar fat content.

From the nutritional point of view it is to be expected that milk whose major constituents (or any of whose major constituents) are lower in concentration than in mixed herd milk would be lower in energy value. That this is true is apparent when one compares the calculated energy values of the monthly average with those of herd milk of similar fat content. It will be seen that the milk of low curd tension

on the average was from 5 to 6 per cent lower in energy value than the herd milk—This was significant in compounding formulas for infant feeding as will be seen later (Chineal Study)

While there was considerable variation in the percentage of ash in the milk, yet the average values approximate closely those accepted as normal for the breed From the nutritional aspect, little or no significance would be attached to this variation since it is known that cow's milk is abundantly nich in mineral constituents, and that the elements, calcium and phosphorus, are almost universally present in a constant It is recognized, however, that the mineral constituents do play an important iôle in connection with the buffer capacity of milk, espe cially as regards acidification 6 Electrometric titrations were made on representative samples of this low tension milk, and buffer curves were drawn Buffer index values vary according to the PH at which they are determined, but it was considered that the buffer capacity from the original PH of the milk to a PH nearing that of an infant's stomach at the height of digestion might be of some value clinically. Gonce and Templeton' have indicated that the latter value approximates P<sub>H</sub> 3.75 Our buffer curves indicate that the buffer capacity of cow's milk is greatest between a PH of 52 and 57 which is in agreement with that recently reported by Holm, Webb and Deysher 8 For the sake of comparison with the results of the latter workers, the average buffer capacity from the original P<sub>H</sub> of the milk to P<sub>H</sub> 47 was calculated The value of 00191 for the low tension milk, 00211 for the milk of two normal Holstein-Friesian cows, and 0 0196 for milk admittedly low in buffer capacity, the latter two values being reported by Holm, Webb and Devsher, indicate that this low tension milk is considerably below the normal milk of the breed in buffer capacity. A further comparison, shows that, whereas it required 52 e.e. of tenth normal hydrochloric acid per liter to reduce the PH of the normal Holstein milk from the original PH to PH 47, only 46 cc were required to effect a similar change in Similar differences would be expected if the the low tension milk acidification were continued to PH 375

Table II illustrates what is to be expected when various feeding formulas, with and without heat treatment, are subjected to the curd test. The heating was done over a rapid electric heater, and excessive loss of moisture was prevented by the use of an air condenser. Karo itself appears to have little or no effect on the curd tension of raw milk, while dilution, as is to be expected, exerts a pronounced lowering, especially at the dilutions greater than 10 per cent. The effect of heat on the proteins of milk is reflected very distinctly in the marked lowering of the curd tension by the boiling for 3 minutes and 10 minutes, the longer period of heating having little or no advantage over the shorter. The effect of boiling is mereased with increased concentrations.

of Karo, due in all probability to the increased boiling point of the mixture. In the case of the reconstituted evaporated milk neither dilution nor heating everts an appreciable effect on the curd tension.

#### CONCLUSIONS

- 1 Although different cows are known to secrete milk of varying curd tension, it has not been our experience that an individual cow invariably continues to secrete milk of a uniform curd tension throughout the major portion of her lactation period.
- 2. The prevailing opinion that normal milk of low curd tension is low in solids not fat, notably in proteins, has been confirmed
  - 3 Normal milk of low curd tension is low in energy value
- 4 The buffer capacity of normal milk of low curd tension is less than that of milk of average composition
- 5 Milk of low curd tension may be entirely normal with regard to physicochemical properties such as rate of remun coagulation, and  $P_{\rm H}$  as well as in bacterial flora.
- 6 The heat treatment accorded the various formulas in connection with infant feeding is effective in producing a mixture of very low curd tension, at least as far as average market milk is concerned. Prolonged boiling appears to have little or no advantage over the shorter period. The heating of mixtures in which evaporated milk replaces the raw milk is not effective in lowering the already very low curd tension of the mixture.

#### PART H CLINICAL APPLICATION

The feeding of infants on the soft curd milk was carried out in the nursery for newly born at the University of California Hospital and at the Babies Aid Foundlings Home Both institutions are located in San Francisco While the period of observation in the nursery was relatively short many of these babies are discharged as foundlings to the Babies Aid where they may remain for some time awaiting adoption. One of us (M.M.) being in charge of the latter institution observations in both institutions could be made by the same physician over a group of infants for a period of six weeks to six months. Infants not born in the University Hospital but admitted to the Babies Aid were also given this special feeding. The age on admission of this latter group varied from six days to two months These infants were under observation for two to eight weeks. Under the physician s guidance the same nurses aided in making certain observations as they weighed fed, and cared for these ba bies It was felt that this arrangement made for much more reliable and uniform conditions than would obtain in the average clinic or out patient department. It was also obvious that in contrast with the group reported by Elias our age group was limited to that important period in infant feeding under eight months. Included in the study were

babies whose initial feeding had not been under our direction, whose inheritance was not the best and whose environment had been poor. The variation in birth weight and lowered resistance to infection must be considered in reference to conclusions. Comparison, however, is made with much the same type of baby fed on evaporated and certified milk formulas.

We observed 60 babics on soft cuid milk, but as brought out previously, the length of observation varied considerably. To make our results of any value we seemed the help of a trained statistician. At her suggestion it was decided not to include the findings during the flist week in the cleven cases which were put on soft cuid at birth. The small number of calories consumed the first few days, and the initial loss of weight, were elements which would affect our conclusions. The

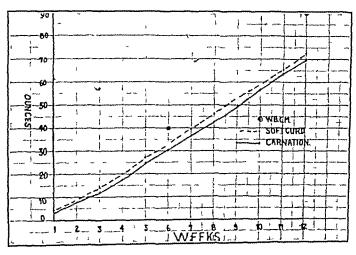


Fig 1

observations during the first week of life on babies started on soft cuid milk before the eighth day have therefore been discarded in order that these cases might be included in this statistical study. For this same reason the cases followed longer than 56 days were also omitted as the number was so small that the statistical data would be rendered unreliable. These statistical studies have consequently been limited to a consideration of 44 cases observed over a seven week period. In our histograms for comparison these regulations were also taken into consideration

The average age of the start for infants fed on soft end milk was 177 days with in average weight of 7 pounds,  $6\frac{1}{2}$  owness. That of infants fed on evaporated milk was 199 days with an average weight of 7 pounds, 9 ounces. Therefore, on the whole, these children had recovered their birth weight. (Fig. 1)

#### DISCUSSION

The graph in Fig 1 shows a slightly greater constant gain, for infants fed on soft curd milk than for those fed on evaporated milk. Al though our data on undiluted boiled certified milk covers the period

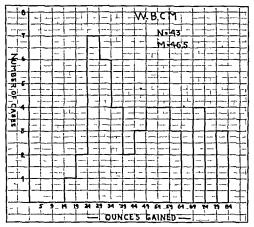


Fig. 2 Graph 1

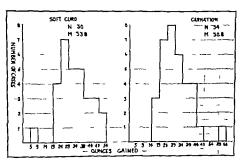


Fig 2. Graph 2.

including initial weight loss, which is not included in either of the other groups and is hardly comparable, the gain in weight for the babies thus fed was much greater than for those fed on either soft curd or evaporated milk. The apparent difference in the gain of weight, of in fants fed on soft curd milk over those fed on evaporated milk, has

been tested statistically by the standard deviation of the difference of means. It was found that this difference is insignificant, because the expected difference is greater than the observed difference.

The histograms (Fig 2) of the distribution of the total gain of weight on the different formulas are offered for comparison, although as was mentioned previously, our series on the undiluted boiled certified milk formula is not altogether comparable, as it includes the initial loss of weight after birth (Fig 2, Graph 1)

From these histograms of weekly gain distribution the following are to be observed

- 1 A very good distribution of weekly gain in weight by infants fed on both soft curd and evaporated milk
- 2 A slightly greater constant gain for infants fed on soft curd than for those fed on evaporated milk
- 3 The range of variation for evaporated milk babies is apparently less than it is for infants fed on soft curd milk
- 4 With the exception of one case fed on soft curd milk there were no losses after the fourth week for either type of feeding
- 5 An interesting observation is that eight cases or 18 per cent out of 44 infants fed on soft curd milk showed a loss of weight during some one of the six weeks, and that 14 babies or 33 per cent out of 42 evaporated milk fed infants showed a similar loss

From a clinical point of view the infants on soft cuid milk gained as well as a similar group on evaporated milk, but not as well as those on undiluted certified milk. The gain was usually gradual, and con-It was exceptional if a loss was incurred after the child was well started However, from our clinical experience in infant feeding the group as a whole impressed us as being consistently hard to start artificially, when one took into consideration weight, comfort, and satis The babies were always hungry until they received from 42 to faction 95 calones per pound of weight or an average of 58 calones the exception for a patient to be satisfied before receiving from 2 to 3 ounces of milk per pound of body weight To make up the caloric intake necessitated adding from 8 to 11 per cent of earbohydrates This increased requirement was also noted by Elias It may also be explained by the lower energy value as reported in Part 1 reason for this higher feeding might also relate to the more frequent The average number of stools was from 4 to 6 a and copious stools day, always soft and voluminous They had the characteristics of a mother's milk stool, like scrambled eggs with soft fat curds however, became smoother in consistency as the baby became accustomed

<sup>\*</sup>The real difference is 338 minus 308 which equals 3 and the square root of the difference of these means is 554 Therefore, the difference in the variation around the mean as great as this could be expected within the realm of probability i.e., in any series of cases under similar conditions one might expect to find as great a variation as was found in these cases

to the formula Contrary to the results of former observers the ma jointy of our babies or 791 per cent, passed large protein curds in the stool at various times although their discomfort seemed in no way related to the passing of these curds. Regardless of the increased num ber of stools and the amount of carboliv drates in the formula, exceptation of the buttocks was not observed

In the beginning we felt that these babies had more gas than the certified milk infants this being the reason for their discomfort. As our experience increased and the infants were given more to cat, this discomfort diminished and gas became a negligible factor. It has been claimed that because the curd of low tension milk is soft and flocculent it is possible to give this milk undiluted and unboiled to the youngest baby, even to a weak premature baby. This may be a fact, but it is surprising how long the average baby took to accommodate himself to this milk, three weeks often passing before he was satisfied. We have fed about equal numbers on diluted and undiluted formulas, 22 of the former and 18 of the latter and find no appreciable difference. This is somewhat surprising if curd tension is so large a factor in the digestibility since dilution reduces still further the curd tension of milk (see Table II) Four of the babies who failed to gain and were un happy on undiluted milk became comfortable and immediately gained when the same formula was diluted Our intention was to use only un boiled milk but on losing two babies after a 24-hour illness, sixteen cases were put on boiled diluted milk. The babies taking this formula were happy and satisfied and gained as well as the babies of the other two groups. It might be of importance to note that the stools in this group numbered only one to three a day and were much firmer and smoother

The impression regarding tissue turgor was that babies who did well on soft curd milk invariably had hard and firm tissues. This might be due to the relative amount of lactalbumin which is theoretically of greater nutritional value (See Table I)

#### SUMMARY

A group of 60 infants ranging from birth to six months of age were fed on soft curd milk for a period of time ranging from 2 to 8 weeks. For statistical study the results of 44 infants thus fed and observed over a soven week period were compared with results in similar groups fed undiluted boiled certified milk and dutted evaporated milk formulas. Histograms are presented for graphic comparison. When fed to the point of sat infaction, infants require more soft curd milk than ordinary cow's milk, due probably to the lower energy value of the former.

Clinical impressions suggest that while not superior to other accepted formulas soft curd milk is difficult to start, but when well started is

very satisfactory and results in excellent tissue turgor. The stools of infants on soft curd milk are more frequent than those of boiled, diluted cow's milk and may often contain large casein curds

#### CONCLUSIONS

Considering (1) the variability in the production of soft curd milk and the increased observation necessary in its production, (2) the lack of superior results when used in comparison with other accepted infant formulas, soft curd milk does not warrant special production and certification for use in infant feeding

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#### POSTVACCINAL ENCEPHALITIS

# DANVILLE, VIRGINIA

#### HISTORIC AL.

IN 1905, Comby of Paris reported a case of encephalitis following vaccination. In 1912 another case was reported in the London Hospital Mader reviewed a case observed in Germany in 1912. Lucksch of Prague in 1924 called attention to cases of supposed epidemic encephalitis following antismallpox vaccination. In 1924 Bastinanse of Holland observed his first case. Five similar cases were observed else where in Holland in the same month. In February, 1929, Wirsina of Denmark reported 11 cases of severe cerebral disturbances following vaccination. In the same month Levaditi of the Pasteur Institute Paris reviewed over one hundred cases occurring up to that time in Europe. The most severe outbreaks have arisen in Holland and England.

From the report of the Smallpox and Vaccination Commission of the International Office of Public Hygiene<sup>1</sup> the following more recent data concerning the distribution of posts accinal encephalitis were obtained

During 1923 1927, 139 cases of disease of the central nervous system following vaccination were described in Holland, of which 41 patients died. Many new cases have been reported since then. The ratio for the years 1923 1927 was one case to five thousand vaccinations with a fatality of one in three. For the first six months in 1928, the proportion was one case for each twenty eight hundred vaccinations. For a period of five weeks, a vaccine from a country in which no case of postvaccinal encephalitis had been reported was used. A case of curred, however, with this lymph in spite of the small number of vaccinations. The available data for England totaled about 130 cases. The ratio was one for forty eight thousand vaccinations.

The report of a Commission in Germany covers a total of 102 cases. During the four year period under consideration for each million per sons vaccinated the first time there were nineteen disorders of the nervous system following the vaccinations with seven deaths. For each million persons revaccinated there was only one disorder of the nervous system with a fatal issue.

Sixty five cases were reported in Austria. Twenty of these occurred in Vienna alone among 39 000 vaccinations. Twenty nine cases occurred in Norway. 13 cases in Sweden, several cases in Czechoslovakia a few cases in France and Switzerland, two cases in Soviet Russia one case in Portugal, and one case in Jugoslavia. No cases occurred in Belgium. Spain, Greece, Italy, Poland, and Rumania.

case has been reported from Canada, and one from South America since the report of the Smallpox and Vaccination Commission of the International Office of Public Hygiene

The wave of this serious complication of vaccination began to recede gradually during the year 1929 References in the literature to new cases during the years 1930-1932 are scanty

According to the delegate from the United States, as reported at Session of May, 1930, of the Permanent Committee of The International Office of Public Hygiene, the total number of cases in the United States was about 20 Armstrong states that 71 cases were recorded in the United States during the past ten years. Gordon and Rhea recorded a case of postvaccinal encephalomyelitis in July 1932. Rochm reported a case in December, 1932, which he had observed in September, 1930. My own case, which occurred in February, 1930, is reported for the first time in this article. This would make a total number of 74 reported cases for the United States.

It is now thought that serious nervous complications of antismallpollocination have occurred in the past without having been recognized as such. In Germany an attempt has been made to reconstruct a great many such cases from the clinical and mortality records of vaccination cases. Some cases of postvaccinal encephalitis in the past are now believed to have been mistaken for tetanus.

# ETIOLOGY

Since antismallpox vaccination constitutes the keystone in the arch of preventive medicine, one would expect a great deal of research and speculation on the cause of such a serious nervous complication as postvaccinal encephalitis and myelitis

The early cases in Holland and in other continental countries occurred at a time when epidemic encephalitis was prevalent. It was thought that localization of the virus in the cerebral tissue inhibits the defensive power of the latter. This inhibition may unleash an encephalitis of the epidemic type in carriers or persons who already have a latent phase of the disease. It is a well-known fact that vaccine virus has a peculiar affinity for nerve tissue. Vaccine virus was demonstrated in the brain tissue in patients with encephalitis and also in patients who did not develop encephalitis.

Research by many investigators proved that the vaccine virus itself is not the cause of encephalitis. A neurovaccine, consisting of an emulsion of smallpox virus cultured in vivo in rabbits' brains, was used extensively on thousands of children in Spain without a single case of postvaccinal encephalitis. In Holland, one hundred and ten different kinds of lymphs were used and cases of encephalitis occurred after forty one of these

The Committee appointed by the Minister of Health and the Medical Research Council in England, under the chairmanship of Sir Hum-

phrey Rolleston, to report on the preparation and standardization of lymph, methods of diminishing or removing the risk of vaccination, and the best method of protection does not incriminate any particular lymph. However, it is held that the vaccination virus, whatever its past history, and in whatever medium incorporated, initiates the nervous disturbance. A local individual predisposition to nervous disorders—in the widest sense of that term—is responsible for the unpleasant sequel to vaccination. This is as far as the British report goes.

An observation published later than the British report would seem to strengthen the theory that a local individual predisposition is re sponsible for postvaccinal encephalitis. Reisch's observed 2 fatal cases of postvaccinal encephalitis showing the characteristic histologic pic ture. During life these patients had myocloma affecting most of the voluntary muscles. A careful investigation of about 300 children in the same neighborhood revealed the presence of myocloma in many and in both the vaccinated and unvaccinated children to an equal extent

Netter who has thoroughly studied this question discussed this subject before the Academy of Medicine in Paris. The disregards the conception of some authors that a contaminated vaccine might be the cause of the encephalitis and likewise, the views of others, who as sume that a virus existed previously in the brain of the subjects and was enhanced in virulence by the vaccine. He contends that it is a question of an attack on the brain by the vaccinal virus which can occur only in subjects with a nervous system that is particularly susceptible, and with a very active vaccine

In 1927, when postvaccinal encephalitis occurred in alarming frequency in Holland the law which decreed compulsory vaccination was temporarily revoked and a committee was appointed to study the cause of this complication and the ways to combit it. The Committee published a report in 1932 which contains a thorough survey of encephalitis postvaccinalis. Several hypotheses have been investigated but no solution to the problem has been found. Encephalitis occurred with all kinds of lymph. Animal experiments to produce postvaccinal encephalitis failed.

In the discussion of the etiology two hypotheses are especially stressed. First that the condition is due to the activation of a latent virus. Second that the vaccine virus itself causes the disease. Neither can be regarded as proved. With this it seems, our present knowledge concerning the causation of postvaccinal encephalitis rests.

Lemer of Vienna advanced the theory that encephalitis following vaccination was due to cerebral metastases. Weichsels cites a case in a child aged eighteen months who developed a generalized vaccinia and encephalitis nineteen days following vaccination. This case is offered as a confirmation of Lemer's theory.

# TABLE I

RESULT	Died	Died	Died		Died	Recovered	Montal de	Died	Dred		Recovered	Recovored	Recovered	
DURATION OF ITTNESS		19 days Died	17 days		14 days			4 days	15 days		16 days	28 days	26 days	
PARALATIC SYMPTOMS		Immobility	Spatieity of extremities	Left hemiplegia	Spartic hemiplegin Cranial newe pulsies	Internal strabis Contracture of upper limbs	General muscular rigidity	Weakness right arm and leg	tion Proms right up Spasm of left side of body 15 days Died	Weakness of left leg		Freigl paralysis left side	Spusm of extremines	
EYE 81 11PTO 11S			Photophobia			Internal strabas		Upward rota tion and fixa	tion Ptosis right up	per na Both eyes turned to	rıglıt		Internal strabis	of upper
REPI B\E9			Increased					Absent			Anomalies	Апотапез		
LFTIIARAA UNCON BCIOURNESS		Lethurgy				Lethurgy		Unconscious Absent	Lethargy	Unconscious ness	Letliargy	Unconscious Anomalies	Lethergy	
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### CLINICAL MANIFESTATIONS

According to Flexner," the two immediately arresting features of postvaccinal encephalitis are its hyperacute course and its high fatal ity. Prodromes including headache, vomiting, and pyrexia, plus paralysis, are regarded by the English as the cardinal symptoms of post vaccinal encephalitis.

According to Armstrong<sup>2</sup> rigidity of the neck has been quite constant in American cases. The local vaccinal reaction has no peculiar character in the children who develop encephalitis

Until recently it was believed that the occurrence of encephalitis after vaccination which locally had no result ie, a vaccination with out a successful local take' could be excluded. However, the disease was described's in a child aged thirteen years, which began five days after a revaccination and which was characterized by respiratory and nervous symptoms without any local reaction from the vaccination. After four days, the child died. Examination of the nervous system demonstrated lesions greatly resembling those found by others in cases of encephalitis postyaccinalis.

Recovery, when it takes place tends to be complete. The outcome is independent of the stormy course and alarming character of the disease at the outset. Sequelae are very rare and are in striking contrast with the end results in cases of epidemic encephalitis of all grades of severity.

The clinical picture is not uniform. It may be that of tetanus, tuber culous meningitis, poliencephalitis or an obscure form of general in toxication not typical enough even to suggest encephalitis.

The recorded observations on 13 cases of postvaccinal encephalitis are presented in tabular form

### PATHOLOGY

The pathologic fludings in the brain and cord establish postvaccinal encephalitis as a clinical entity. According to Flexner\* even the gross appearance of the brain and cord in postvaccinal encephalitis differs from epidemic encephalitis. The lesions as disclosed by the micro scope are more impressively distinct. The characteristic type of lesions in epidemic encephalitis is proliferative and infiltrative.

The findings in postvaccinal encephalitis consist of adventitial and periadventitial round-celled infiltrations distributed throughout the brain and cord. With appropriate staining methods, areas of myelin degeneration may be seen centered about the smaller vessels, which gradually fade into normal myelin structure. The characteristic soft ening or microglia proliferation about the blood vessels of the white substance of the central nervous system resembles the action of a toxic substance.

As compared with epidemic encephalitis, in which the lesions are nearly always confined to the brain, and chiefly to the basal gray matter, with much rarei involvement of the cortex and white matter, post-vaccinal encephalomy elitis is a disease in which both brain and spinal cord and both the gray and white matter of each, are implicated, and in which the white matter is attacked by preference. The brain and cord are diffusely affected, often without any particular choice of locality, though not everywhere with the same intensity. The lesions in the spinal cord are as important as those in the brain, if not more so

It is a remarkable phenomenon that with lesions so widespiead and severe in fatal cases, complete functional restoration takes place, as a general rule, in those that recover

There are no characteristic blood and spinal fluid findings in this disease. German observers found smallpox virus in the blood of 8 children between the third and tenth days after vaccination with reaction, and absent from the blood of 9 others. None of the spinal fluids obtained from the children contained virus, even when it could be demonstrated in the blood. The spinal fluid of one of the three infants with symptoms of postvaccinal encephalitis produced by the same vaccine, contained virus on the twelfth day after vaccination. The reports of other observers on the spinal fluid show essentially negative findings. The fluid is sterile, and at times, increased in pressure. There may, or may not, be a slight increase in the cell count. One case showed one hundred and seventy-nine cells per cubic millimeter. Tests for globulin were normal in some spinal fluids, while negative in others. Qualitative tests for sugar were positive in all the spinal fluids tested.

According to a Dutch authority,12 the following points characterize postvaccinal encephalitis and differentiate it from epidemic encephalitis

# EPIDEMIC ENCEPHALITIS

- 1 Thick layers of lymphocytes and a certain kind of plasma cells in the peri vascular lymph spaces
- 2 Neuronophagia by glia cells, of which only a few were changed into grinulated cells
  - 3 Preference for the grav substance
  - 4 Diffuse spreading
  - 5 Preference for the brain trunk

# POSTVACCINAL ENCEPHALITIS

- 1 Accumulations of microglial granulated cells outside the periodscular lymph space in the nervous tissue itself
  - 2 No neuronophingia
- 3 Strong preference for the white substance
  - 4 Spreading in concentrated heaps
  - 5 Preference for the hemispheres

# PREVENTION

Considering the number of antismallpox vaccinations performed vearly the chances for serious nervous system complications are infinitesimally small. However the total number of such complications

is rather impressive, and may serve as a tool in the hands of various antivaccinationist elements. It may justifiably cause some concern to the regular medical practitioner

While the problem of etiology is still unsolved, yet sufficient facts of epidemiologic nature have been accumulated to constitute a rational basis of prevention

The important fact has been noticed that in countries where vacci nation is practiced in infancy none, or very few cases of encephalitis, have developed. Also the number of cases of encephalitis following revaccinations is smaller than that following primary vaccinations On the basis of these facts the English Committee recommends that primary vaccination shall be performed in infancy between the ages of two and six months and revaccination at the time the child enters school, five to seven years and again on leaving fourteen to sixteen In place of the officially advocated four insertions, trial shall be made of vaccination and revaccination in one insertion scarification and cross hatching are depreciated The Minister of Health is of the opinion that it is not generally expedient to press for the vaccination of persons of school and adolescent age who have not previously been vaccinated, unless they have been directly exposed to infection

Sixty six per cent of all cases of postvaccinal encephalitis in England occurred between the ages of five and fourteen. Seventy nine per cent occurred in persons between the third fourth and fifth year of life. Infants under one year of age are relatively nonsusceptible to postvaccinal encephalitis.

In Holland, during the period covered by the report among 14 038 vaccinations from birth to one year 1 case occurred. Among 32 865 vaccinations between the ages of one and two years, 1 case occurred. In 1879 vaccinations between the ages of one and eleven years, 1 case occurred. This confirms the relative nonsusceptibility of young children.

In the countries where postvaccinal encephalitis occurred, it af fected children mostly of school age, only rarely has a case occurred in infants under two years

Knoepfelmacher states that not a single case of postvaccinal en cephalitis has occurred among persons vaccinated by the intradermal method of Leiner However it was impossible to ascertain the num ber of persons who were vaccinated by the intradermal method of Leiner on the basis of which the conclusion of Knoepfelmacher was made

In connection with prevention of postvaccinal encephalitis, the work and views of Armstrong<sup>1</sup> merit the widest circulation and extensive clinical application. What follows is a condensation of the views of Armstrong

Judicious exercise is essential for the fundamental well-being of familiar tissues, even to the bones and teeth. It may be assumed that the same is true of those tissues which constitute the defense mechanism, whatever and wherever they may be. Aimstrong decided to determine whether preliminary immunization by the injection of non-specific antigens might increase temporarily an animal's efficiency in its reactions against a subsequent inoculation with vaccinia. This conception squares fully, or is identical with, the principle of non-specific protein theory. The parenteral administration of a nonspecific antigen influences a subsequent infection. Similarly, an acute infection may favorably modify the course of a chronic infection. The "nonspecific" stimulation of the defense mechanism constitutes the evercise for the defense mechanism which may be utilized therapeutically and prophylactically

Aimstrong attempted to verify experimentally the hypothesis that previous nonspecific inoculations would render an animal's response to vaccinia more efficient. He made use of a strain of vaccine virus developed at the National Institute of Health, which was capable of producing a fatal meningo encephalitis when introduced into the brains of white mice. A dose of virus was selected through preliminary titration which was slightly less than sufficient to kill all of a group of normal mice. Preliminary to the intracranial inoculations with the most fatal vaccine virus, the mice were immunized against various antigens, diphtheria to old having been mainly used as the antigen. He then compared the number of deaths among previously immunized and nonimmunized groups following intracranial inoculation with vaccine virus. In each experiment, mice for the test and control groups were from the same shipment, and were placed under identical conditions.

The investigation showed that there were more survivals in the toxoid-immunized groups than in the other groups, and that the toxoid-treated mice tended to die later than the controls. The results indicated that the protection afforded by a previous nonspecific stimulation is only relative, and not absolute. However, the test was a very severe one since the vaccine virus was injected into the brain tissue itself thus shunting out whatever mechanism there exists for protecting the central nervous system against vaccine introduced by other routes than into the central nervous system itself.

While the protection of a few mice from a cerebral virus infection by means of a previous nonspecific stimulation of the defense mechanism does not necessarily lead to the conclusion that children could similarly be protected from postvaccinal encephalitis, yet the conception on which the work of Armstrong is based, and the limited amount of experimental laboratory evidence to support it, is sufficiently sound to accept its implications in practice Armstrong recommends that primary vaccinations, especially after the first year of life, be deferred until contemplated immunization against diphtheria or other diseases has been accomplished. The recent preliminary exercise of the immunity or defense forces may lead to a more efficient antivirus response with the result that the ensuing reaction may tend to simulate primary infant or secondary vaccinations in their comparative mildness and freedom from post vaccination reactions

Since immunization against diplitheria is now almost universally practiced in this country it would be of value to put Armstrong's ideas and work to the widest clinical trial

### TREATMENT

In the absence of a definitely established cause of postvaceinal encephalitis, treatment must necessarily be empiric. Epidemiologic observations, however, furnish us with some facts on the basis of which certain broad prophylactic measures may be formulated. From the reports of the various commissions on this subject the following is adduced with regard to prophylaxis.

- 1 Postvaccinal encephalitis is much less frequent in voung children than in older children
  - 2 No person should be vaccinated unless he is in perfect health
- 3 Primary vaccination should be performed during the first year of life
- 4 Secondary vaccination should be performed after ten years of age
  - 5 Attenuated vaccines should be used
- 6 Only a single superficial skin insertion or puncture should be done with a minimum of trauma
- 7 When a postvaccinal central nervous system complication follows it is infinitely less grave when it follows a vaccination made during the first months of life

Therapeutically favorable results were reported from the use of blood serum from recently vaccinated persons. However the good results were not always uniform. Hekman's had the opportunity to observe the therapeutic results of blood serum treatment simultane ously in two children aged two and four respectively. When the child aged two was admitted to the hospital seven days after being vaccinated with cowpox, it had spasms over the whole left side of the body. Both eyes were turned constantly to the right, also the head During the attacks the face was pale and cyanotic. The child was unconscious, and the pulse was rapid—about 140. On the left upper arm were three distinct pox pustules with considerable reaction in the vicinity. The evening of the day of admission, the patient received

an intravenous injection of 10 cc of blood serum from the mother. who had been vaccinated at the same time as the child ing day, the injection was repeated. The morning of that day the patient had still a few attacks, but toward noon they ceased child was, however, still unconscious, but the temperature began to fall, and in two days it had become normal Twelve days later, the natient was dismissed as cured The other child, aged four, received similar treatment but died, in spite of repeated injections of serum

The British Report contains numerous observations on the efficacy of serum treatment While serum treatment should be undertaken in every case, the exceptions are too numerous to regard it as a spe cific measure

# CASE REPORT

J L, five years of age, third child Full term, normal delivery Birth weight, eight and one half pounds Brenst fed History of whooping cough, measles, chickenpox, and occasional attacks of tonsillitis.

The child was vaccinated for smallpox on January 24, 1930 One or two days after vaccination, he began to complain of pain in his stomach and head, but he had no fever Three days after vaccination, he began to vomit There were no diarrhea, fiver, chills, or cough He lost weight rapidly, and gradually began to ap pear indifferent and drowsy. He complained of pain in the back only when moved

The child was first seen Feb 7, 1930, two weeks after vaccination well nourished boy, but somnolent, and answered questions slowly and with difficulty Examination revealed a scaphoid abdomen slightly positive bilateral Kernig signs, neck very rigid and painful on moving, generalized hyperesthesia of skin, internal strabismus and ptosis of right upper lid, pulse rate about seventy five. Urinary findings were negative

Lumbar Puncture Eighteen cubic centimeters of clear fluid were withdrawn under considerable pressure (ell count, one and one half hours after withdrawal, was 15 to 20 per cm, consisting entirely of lymphocytes. Tests for globulin were Qualitative test for sugar was positive. Ophthalmoscopic examination reveiled normal eyegrounds.

Twenty six days after the onset of symptoms, the Child gradually improved child was well with the exception of slight prosis of the upper right lid, which dis appeared a few months later

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# PHRENIC NERVE PARALYSIS IN THE NEWBORN, ASSOCI

# JACOB L STIEN MD BROOKLIN N I

UNILATERAL paralysis of the diaphragm in the newborn has been but rurely reported only nine such cases being found in the liter ature. Of these, seven alone were associated with simultaneous paralysis of the brachial plexus

Weigert in 1920 collected thirty cases of unilateral phrenic nerve paralysis from the literature, with one of his own, but only two of these were in newborn infants, and in no case was there verification by fluoroscopy

It is not my purpose to discuss paralysis of the diaphragm in older children—due to tuberculosis, trauma, pressure on the phrenic nerve from various causes, diphtheria, or poliomyclitis—but to confine this study to the type of paralysis affecting the newborn. Accordingly I have brought together all reported cases tabulating and summarizing them for ready reference. To the cases reported two are added that have come under my personal observation.

The phrenic nerve, which is principally motor, has its origin mainly in the fourth cervical nerve, but receives additional fibers from the third and fifth ecryical nerves, this last named association bringing it into the domain of the brachial plexus among the supraclavicular branches of which is one which communicates with the phrenic nerve The nerve runs down the neck on the scalenus anterior muscle crossing this from without inward, and at the base of the neck accompanies it between the subclavian artery and vein Entering the thorax it passes over the root of the internal mammary artery from within outward then follows an almost vertical course downward over the aper of the pleura and through the superior and middle mediastina to the upper surface of the diaphragm which it supplies with muscular branches The right phrenic nerve is shorter than the left because of its more direct downward course and the greater elevation of the diaphragm on that side. Both nerves break up into terminal branches before reach ing the thoracic surface of the diaphragm some of the branches of the right nerve the phrenicoaldominal traverse the diaphragm and pass to the muscle from the under surface

From our knowledge of its anatomy, it is easy to understand how in a typical case of Duchenne Erb's paralysis the phrenic nerve may

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readily be damaged at the same time that the plexus has been injured at birth, whether the lesion be due to difficult or forceps delivery or to breech delivery

# REPORT OF TWO CASES

Case 1 —Baby K, a bov, weighing 9 pounds 8 ounces at birth, which was by breech delivery, was seen at the office two weeks after delivery, June 21, 1928, suf



Fig 1 Case 1

fering with a cough and dyspner. Physical examination revealed a large, well nourished infant, with a Duchenne Erb's paralysis on the right side, together with a hematoma of the sternocleidomastoid muscle. No examosis was present. The respiration was rapid, and there wis slight dullness at the bise of the right lung, with diminished breathing. No rules were heard.

On fluoroscopic examination the heart was seen to be pushed somewhat over to the left side. The diaphragm on the right side appeared high and exhibited the characteristic "paradoxical movement" first observed and named by Kienhock in 1898 in a case of propneumothorax. The right half of the diaphragm moved

up with inspiration, contrary to what occurs in normal respiration, while the left half moved down in the usual way thus showing a typical sec-saw action, since known as Kienbook s phenomenon. Rountgenograms of the cheat at this time revealed that the right diaphragm was markedly raised being at least two intercontal spaces higher than the left and that the abdominal viscera were raised proportionately with it, while the heart was slightly displaced to the left. There was no evidence of diaphragmatic hernia. Repeated fluoroscopic examinations showed that within one month the diaphragm had receded to its proper place. One year later roentgen examination revealed a completely normal relationship between the right and left sides of the diaphragm. The child has subsequently developed normally in every way and the Erb's palsy has entirely cleared up

Case 2.—Baby L. M., a case of high forceps delivery, with weight 7 pounds 2 ounces at birth, was brought to the office two weeks later with a history of granosis. The essential physical findings were as follows Right-sided Duchenne-Erbs paralysis, slight cyanosis rapid respiration duliness and diminished respiration at the right base, no rales. Fluoroscopic examination revealed that the dia phragm on the right side was at least two intercostal spaces higher than on the left with the characteristic see are action of the diaphragm Roentgeongrams confirmed these findings. One month later under fluoroscopy the diaphragm was seen in its normal position. Repeated examinations at subsequent dates showed a complete recovery from the right-sided Erbs palsy and the right phrenic nerve paralysis.

### REVIEW OF THE LITERATURE

For convenience in summarizing the cases found in the literature, I have taken as a basis the tabulation drawn up by de Bruin, making the necessary additions to include four more recent cases, and omitting the cases of Weigert (1920) and Dyson (1927) which do not properly belong here, since in neither of these was there an associated paralysis of the plexus. Incidentally however these two cases refute Epstein st assertion that injury to the phrenic nerve without concurrent involvement of the brachial plexus has never been cited in the literature, and that one cannot conceive of such a phenomenon. Dyson st case was accounted for by the fact that in cutting through the umbilical cord which was wound several times around the neck the latter was accidentally incised with direct injury to the phrenic nerve resulting in paralysis of the diaphragm without an associated Erb's paralysis. Why in Weigert st case the nerve alone should have suffered without the plexus sharing in the paralysis has not been explained.

A glance at our table shows at once that in every case the twofold paralysis followed a difficult labor or one with some abnormal feature. Thus in four cases there was forceps delivery and in five cases breech delivery, suggesting beyond a doubt that the condition was the result of a trauma inflicted at the time of birth. It is worthy of note that the injury was located on the right side in seven of the nine cases—an observation which is of importance for differentiation from relaxatio disphragmatica, which may also exist in the newborn. In all nine cases the diagnosis was confirmed by the reentgen rays.

It was Kofferath, in 1921, who first reported a case of phrenic nerve paralysis in the newborn associated with Duchenne-Erb's paralysis of the brachlal planes.

# TABLE I

I LEVUS PVR ALLYSIS	!	+	+ + + + + + + + + + + + + + + + + + +	d (Soon	thal plexing
RFSULT	Cured after 4 months Gessa tion of piradoxical move monts Diaphragm still a little too high on right side	Death from pneumonia months after birth *	Dia Plevus paralysis, cured in 14 de days. Paralysis of dia phragm Cured after 8 months, confrinced by recent genegram	Under observation until third jenr, 3 attacks of broncho pneumonia Roentgenologie changes persisted	Neither gross nor microscopic changes in phrenic nerve brachlal playing
ROENTGFY FINDINGS	High position of diaphragm on right side, paradoxical move ments Heart pushed to left and downward upon inspira tion	Ligh position of diaphragm on right side Right lialf of di aphragm moderately mos able	Paradoxical movements, phragm ligh on right si	Right half of diaphragm light or by 4 rids than left. Para doxieal movements Entire right lung in sliadow	}
CLINICAL SYMPTOMS	nuthara Dyspace immediately following IIIgh position of diaphragm on Cured after 4 months Gessa reeps hirth Dilated also masi, right side, paradoxical move thoractery of breathing ments Heart pushed to left monts Diaphragm still and downward upon inspira	short respiration Diagnosis right side Right laif of di months after birth preumonia symptoms ap aphragm moderately mor	Attacks of cyanosis Rales Diagnosis pneumonia Prest symptoms appeared after 14 days.	Difficult mediately after birth Right for by 4 rids than left. Phra laif of ehest moved less than advised movements. Entire left half Dullness and weak right lung in shadow changes persisted	Molither atrophic on right side Fewer muscle fibers
BIRTIC	17 yr priniiparn Low forceps Episiotomy	Breech presenta tion Test Smellia	Low forceps	Breech presenta tion Difficult labor	mem atrophic on
R. OR	æ	H.	<b>~</b>	æ	Dlaphi Atel
	Kofferath (1921)	Landsberger (1026)	rtedmann and Chamber lain (1927)	Epstein (1927)	· \utopay

	¥ 4 4	BIRTH	CLINICAL BYMPTOMS	ROENTUEN FINDINGS	REBULT	PLEXUS PAR ALYBIS
Mulrer (1928)	卢	Forcept. Long tedfous birth.	In this mild case no clinical symptoms.	Movements normal on right side less movement on left. High position of diaphragm on left	Foreog. Long In this mild case no children Movements normal on right Rapid care of N phrenicus and tedious birth. symptoms. High position of diaphragm on left.	+
Remé (1030)	ដ	Primipara, Breech delly ery difficult labor	Rapid breathing exanosis im mediately after birth. Ab- domen contracted on inspira- tion Became exanotic upon crying	Ugh position of diaphragm on loft side Paradordeal move- ments	Rapid breathing eranosts im High position of diaphragm on Regression of plexus parairsis mediately after birth. Ab- loft side Paradovical move- persistence of phremie nerre domn contracted on inspirm ments ments parairs at age of 1 year crying	+
de Bruin (1931)	ρÍ	Second of a pair of twins. Breech presen tation.	Preumonia and pleurisy Raice. Dyspnea.	ligh position of diaphengm on leight side. Heart displaced toward left and downward.	Second of a pair Pneumonla and pleurlay Hâles [High position of disphragm on Little change during 6 weeks of brain. Dyspaea. Dyspaea. Dyspaea. Lead to be been breen present the change of the present the change of	+
Stein (1033)	ದ	Breech dollvery	Rapid respiration Dallness at IIIgh position of base Hematoma of sterno-right side eleldomastoid muscle movements.	High position of diaphragm on right side Paradoxical movements.	Breech dollvery Rapid respiration Dullness at Iligh position of disphragm on Diaphragm lad resumed prop base Hematoma of sterno- right side Paradoxical or place in 1 month.	+
Stein (1933)	전		Cyanosis, rapid respiration duliness and diminished breathing at right base.	High position of disphragm on Disphragm in ne right. Pendorical move after I month. nests.	High forces de Cyanoria, rapid respiration High position of disphragm on Disphragm in normal position livery dalliness and diminished right. Paradoxical move after I mouth, breathing at right base.	+

This author sought vainly in the literature for another case of the same kind. He had noted soon after the birth of the child that respiration was unaccountably labored, and this observation, combined with evidence of injury from forceps at Erb's point, suggested to him that the infant was suffering with traumatic paralysis of the phrenic nerve. It was not until twenty four hours later that the paralysis of the plexus also became evident, through a palsy of the right arm. The fluoro scope confirmed the injury to the phrenic nerve by revealing the classic paradoxical movement of the diaphragm. By the fourth day the paralysis of the nerve had passed, and respiration was normal. The plexus paralysis, however, slower to yield, did not disappear until the end of four months.

Two of the nine cases listed in the table terminated fatally. In that of Lands bergers in which the infant was delivered in breech presentation, pneumonia symptoms supervened soon after birth, to which the infant succumbed at the age of two months. At postmortem the diaphragm was found to be atrophic on the right side, and on microscopic examination it was seen to contain fewer muscle fibers than on the left side. This last finding furnishes definite proof that the case was not one of relaxatio diaphragmatica, which may equally be congenital and may present the same high diaphragm on the fallen side. A study of the phrenic nerve, brachial plexus and spinal cord revealed no changes either gross or microscopic in any of these structures.

In de Brun's' case the infant, who was the second of twins, born in breech delivery, was brought to the clinic at the age of four weeks, with a history of coughing and persistent refusal to take nourishment. A swelling of the sterno cleidomastoid and the presence of a Duchenne Erb's paralysis, both on the right side, together with the fact of a good general condition in other respects, suggested a congenital malformation, until the fluoroscope demonstrated a wide difference in the position of the diaphragm on the two sides with a definite Kienboel's phenomeron and a pushing of the heart toward the left side and downward. The case was under observation for six weeks, and gradual improvement noted, when at the age of four months death suddenly occurred, the cause of which remains unknown since it was impossible to obtain an autopsy

The predominant clinical symptoms of paralysis of the phrenic nerve are cyanosis, dyspinen and other respiratory disturbances, together with disorders of nutrition in less degree. Thus in all cases but one (Mulzer's') the presence of pulmonary symptoms of one or another nature was recorded. In Epstein's case the child, under observation until the third year, suffered three attacks of bronchopneumonia and the rochigenograms showed the lesions still persisting. The low forceps case of Friedmann and Chamberlain's likewise exhibited symptoms of pneumonia, but these did not appear until the plexus paralysis had been practically overcome, at the end of two weeks. Here the paralysis of the phrenic nerve persisted up to the eighth month, as was confirmed by rochtgenogram.

Mulzer 8° ease, one of the two left sided ones, was rather exceptional in that the phrenic lesion was entirely symptomless and might have gone undiscovered in the presence of an Erb's paralysis had not roentgenologic examination brought to light the high position of the diaphragm on the left side

The case of Rem(° one of breech delivery, exhibited rapid breathing, cyanosis on crying and nutritional disturbances, which, according to that author, are of more importance when the lesion is on the left side. The fact of an Erb's paralysis of the left arm led to roentgen examination which revealed the presence of a high diaphragm on the left side and the characteristic Kienbool phenomenon. In this child at the age of three months, the chest was asymmetrical, with the left side more strongly arched than the right. The intercostal spaces were wider, and the ribs

took a more horizontal direct in than those on the right side. When reexamined at the age of nine months the paradoxical movement of the diaphragm and its high position on the left side were still persisting.

#### COMMENT

The climical picture has been well described by Hitzenberger in his special studies on the disphragm. The great danger to which the patient is exposed if the paralyzed nerve does not quickly recover is that of pneumonia. The anis arance of evanosis and dyspnea shortly after an instrumental or difficult birth should lead the physician to suspect in jury of the phrenic nerve. If such is the case physical examination will as a rule reveal soon after birth extensive changes similar to those observed in massive pneumonia or pleurist, but with normal temperature and a good general condition. Fluorescopy will then disclose a high position of the diaphragm on the affected side and a typical paradoxical movement of the diaphragm (Kienbock phenomenon) in breathing the affected side ascending during inspiration while the normal side descends, and the reverse of this in expiration like the see saw appearance of a pair of scales in perfect synchronism. The respiration is irregular and rapid and often there may be severe erises of air hunger. The type of breath ing, unlike that of normal newborn infants is thoracie. In Epstem st case, the affected half of the chest made wider excursions in breathing than the healthy side. The heart is pushed out of place toward the brownerof bur abis bateafli

### SUMMARY

- 1 The rarity of the cases reported arouses the question whether paralysis of the phrenic nerve is not more common in cases of Erb's palsy than has been supposed. The complete absence of symptoms in one of the cases reported confirms such a suspicion. Attempts to check up this phase of the subject have been unsuccessful a number of new born infants having been studied fluoroscopically for possible phrenic nerve injury, but no cases being observed.
- 2 A study of nine cases of phrenic nerve paralysis associated with Erb's paralysis discloses that the great majority of cases are on the right side
- 3 The prognosis is favorable as regards restoration of function in the very early days of life but appears to be less so if treatment is delayed two to three months. Even then the prognosis as to life is not unfavorable as shown by the cases of Reme and Epstein
- 4 Paralysis of the phrenic nerve should be looked for in all cases of Erb's paralysis.
- 5 The suggestion is made that in view of Kofferath having been the first to describe the syndrome of Frb s paralysis with phreme nerve paralysis the name. Kofferath syndrome, he given to the condition

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135 EASTERN PARKWAY

### MY ELOSARCOMATOSIS

# RAITH INTERMED MAD CHICAGO

THE diversity of opinions as to the etiology and character of lence min is fully recognized. Briefly there are two schools of thought those who believe in the infectious origin of lencemia and those who consider the disease a true blastomatous process. In favor of the former are the acute lencemias with abrupt onset septic course and short duration. In favor of the latter are the chronic lencemias with insidious onset progressively downward clinical course and cellular infiltrations in the internal organs (Schultz'). To strengthen the view as to the neoplastic character of certain cases of lencemia are those rare instances of complicated lencemia such as chloroma and lencematic internations in which the accumulation of lencocytes assumes the form and character of timor. Recently I have observed clinically and at autopys an obscure form of disease and have attempted to classify it. I believe this case falls into the group of complicated lencemia and appears to substantiate the blastomatous nature of certain forms of lencemia.

### CASE REPORT

Mistory—M 8 a white bor aged six and a half years, was admitted to Sarah Morris Hospital on March 21, 1931 with the complaints of swollen cyclids and sinus trouble of one week's duration and pain in the stomach of two weeks duration. He was apparently well until December 1930 when he developed a cold and sore throat. One week later he complained of drawing pains in the wrists, elbows and anterior surface of the legs. The following day he experienced pain in the pit of the stomach worse during the night and unaccompani d by anusea or vomiting. This pain disappeared spontaneously in twenty four hours. Three weeks before admission to the hospital he contracted shickenpox during which time the home pains disappeared During convalencence from the chlekenpox the hone pains and epigastric distress returned and persisted off and on up to the time of hospitalization. One week before admission his mother noticed swelling of his right upper cyclid. The following day the left side of his face was immedian and the left upper lid swollen.

The child a past history included measles at two years and frequent sore throats for which his tonsils and adenalds had been removed at the age of four years.

His grandmother (paternal) died of carcinoma

Examination—Examination revealed a well-developed I at poorly nourished extremely pale and emacint d child. His temperature was 1004 R Blood pressure was 108/70 Julse 130 and respirations 30 Sentiered throughout his seally were many round pea to marble sized reddish purple nodules, firm in consistency and

From the Sarah Morris Hospital for Children and the Department of Pathologs of the Michael Reers Hospital Chicago Illinois.

apparently attached to the underlying skull. They were most numerous over the purietal and frontal regions He exhibited a left sided peripheral facial piresis At the middle of the lower margin of the right mandible a small rough bony cleva tion was felt The eves were prominent but did not protrude Both upper hids were brownish pink, swollen and indurated but nonflucturant His lips were dry and his tongue was coated The tonsillar fossae and pharvna were slightly injected anterior and posterior cervical lymph nodes were slightly enlarged, more on the left, and were discrete and firm. The heart and lungs were normal The abdomen was scaphoid and the spicen was palpated just below the left costal margin organs or masses were palpated The genitalia were normal Except for marked consention the extremities exhibited no abnormal findings. The axillary, epitrochie ir, and inguinal lymph nodes were not pripated. There were no pathologic reflexes

I aboratory Data --

TABLE I
BLOOD FINDINGS

DNTF	RBC	HB	и в с	POI Y MORPH	I YMPHO-			BASO PHH FS	IM MATERE RBC
3/25	3 ()	77	6200	44	48	6	2	0	0
1/5	278	77	8000	45	48	6	2	2	3
1/13	~	~	5000	23	68	3	1	2	1
1/15	2.86	77	12 200	45	49	0	2	1	0
1/22	-	_	10000	48	46	G	()	0	2
7/5	2.67	50	12,500	50	11	S	1	()	4

\*Many of the cells classified as hymphocytes were large. The nuclei were purplish in color the chromatin rather dense but not clumped as in the mature hymphocyte which were present and the nucleolar membrane was distinct. The cells contained abundant nongranular sky blue c toplasm in which azurphilic grunules were common (Wright and Clemsa stains) These cells might possibly be classified as hympholdocytes (Pappenhelm)

Chemical evaluation of the blood revealed normal nonprotein nitrogen, sugir, and cholesterol contents. Blood cultures on two occasions showed no growth. The blood Wissermann, Kahn, and the tuberculin tests were negative. Except for be cusional granular casts the urine examination was repeatedly negative. Tests for Bence-Jones protein were negative.

Liopsy of Tumor Nodule of the Stull, April 7—Microscopic examination revealed a new formation of cells extensively inviding the bone and surrounding structures. The cells were small and round consisting of scinty acidophilic extoplasm and round nuclei. The nuclei showed variation in chromatin content. Many mitotic figures were present. Marked vascularization of the tumor growth was present and many of the blood spaces were lined by tumor cells. Necrosis of the adjacent tissue was marked. The impression was that of a malignant tumor. Implies accomatically celled spaceona, or leacosurcoma.

Course—On March 31 very examination revealed a peculiar mottling of the skull particularly in the parietal bones, giving the appearance of hiving been "drilled by fine shot (Fig. 1). The lower third of both femura appeared moth after (Fig. 2). There was also a similar rarefaction of the shaft of the fibula just below the head. Films of the entire pelvis and lower spine exhibited the same moth caten appearance. Films of the right arm disclosed erosion of the shaft of the humorus at the upper part of the lower third and of the ridius below the head (Fig. 3). On April 7 two nodules were removed from the skull for microscopic examination (see biopsy report). The nodules from the skull were reddish purple

in appearance, pea to murble sixed firm in consistency and involved the skin and underlying tissue becombarily many of the nodules had undergone abscess formation. Two such abscesses, one from each cyclid, were incised. Gram positive coecimero found on stained smear. From April 17 to April 20 many more nodules appeared on the scalp and over the back. At this time small shottke axillary and



Fig. 1.—Reentgenogram of the skull showing the moth-eat.n appearance—the thin ning and erosion of the costex.

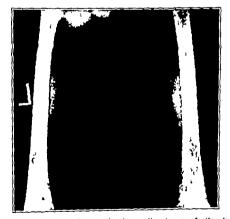


Fig 2.—Rentgenogram of the femura showing moth-enten rarefaction in the distal portions.

inquinal glands were palpated. An x ray of the cless on April 20 revealed no pul monary medians. The ribs, scapular and clavicles showed areas of mrefaction (Fig. 4). On April 27 left propteds was present and the patient complained of pain in the left parient region. On April 27 the patient received the first of several deep x ray treatments to the skull and the long bones showing rarefaction. On

May 12 the bony elevation on the right mandible was enlarged and several more irregular nodules were palpated in the left supraorbital and frontal regions. The temperature had risen to 102° F and the patient had begun to cough. There was evidence of bronchopneumonia in the right lower lobe. On May 20 the patient expired in a state of extreme emicration.

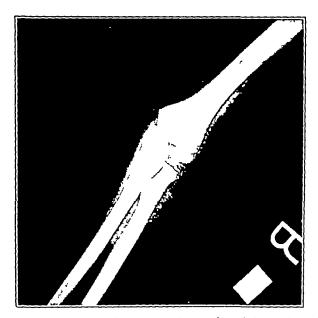


Fig. 3 —Roentgenogram of the right arm showing crosion of the shaft of the humerus and the radius b low the head

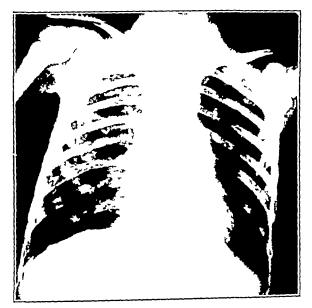


Fig. 4 —Roentgenogram of the thest showing rarefaction in the ribs scapulae and clayleles

### AUTOPSY REPORT

Cross Findings.—The autops: was performed by Dr Otto Suphir pathologist, about four hours after death. The body was that of an underdeveloped markedly enactated made child about six years old. The skin showed many small nodules measuring as large as man in domiter they contained a large amount of yellowish ereany material. Some of these nodules showed shallow ulcerations, a few of which were covered with a reliable brown crust. The skin was very thin and there was little substantageous fat tissue.

The serous envities revealed no abnormalities

The heart showed no gross changes.

Both lungs were air containing. The right lewer lobe showed a few patches of bronchopmenmonia

The liver was larger than normal and of firm consistency. The capsule was smooth. On section the architecture of the cut surface in many portions was obscured. Where visible the central zones were red, depressed and some of them fused by confluence. The periportal spaces appeared bright vellow. No tumors or feucemic infiltrations were visible grossly.

The spiece was slightly larger than normal and of firm consistency. The cut surface was reddish brown. The trabeculae were clearly visible. The follicles appeared small and indistinct

The kidness were enlarged and soft. The capsules stripped away with case leaving smooth surfaces. Throughout the surfaces, a few gray nodules were seen measuring up to 0 mm. in diameter. On section the architecture of the cortex was obscured. Nodules which were also visible in the cut surfaces appeared grayish and well defined. The pelves ureters and bladder revealed no gross abnormalities.

The pancreus and suprarenals revealed no gross changes.

The exoplagus was dilated. The nuces of the exoplagus showed several small ulcers measuring 2 to 3 mm in dameter which were surrounded by a vellowfall necrotic tissue. Throughout the stomnels duodenum and jejunum many nodules were encountered which measured from 3 to 12 mm, in diameter. These nodules secured to have rise in the submucosa and many were covered by nuces with small areas of ulcerations. The nodules were very easily movable from the underlying nuscularis, they were soft light gray and revealed a homogeneous cut surface.

The lymph nodes throughout the body were slightly enlarged and softer than normal. On cut section they were gray and showed a finely granular surface

The skull was much thinner than normal and showed many depressions and lacera tions (moth-caten). Between the calvurium and the dura a large, flat yellowish brown tumor was noted, measuring 2 to 3 mm. in thickness. The tumor extended over the convexity of the brain completely filling the epidural space. It was firmly attached to the dura and could not be removed from the bone. The tumor did not extend into the arachnoidea or brain. The base of the skull showed no tumor growth. Both orbits contained a large amount of edematous fat tissue but no tumor growth.

Multiple acctions of the brain revealed no gross abnormalities

The bone marrow of the sternam and ribs was gravish red. The bone marrow of the right tibia was light grav in some portions more yellow it was much firmer and more compact than normal and showed a finely granular cut surface.

Histologie Fxamination -

Heart Sections of the invocardium showed no changes.

Lungs. With the exception of a bronchopneumonia in the right lower lobe no abnormalities were noted.

Liver The liver cells showed a moderate granularity of the cytoplasm. The liver cells surrounding the central veins contained large fat globules. There was no cellular infiltration.

Spleen The follieles appeared atrophic. There was a slight increase of connective tissue throughout the pulp. The sinusoids were distended and filled with red blood cells. A moderate number of monocytic cells were seen throughout the pulp. No accumulations of lymphocytes were found in any of the fields.

Kidneys The lining cells of the convoluted tubules were swollen, their evtoplasm was finely granular. In many portions the nuclei were absent. Some of the sections showed large accumulations of cells with paucity of evtoplasm, but distinctly out hand, deeply stained nuclei. These cells resembled large lymphocytes. They were found in several sections, but were situated mainly in the cortex (Fig. 5). Giemsa stain revealed that only a few of these cells showed granules in their evtoplasm.



Fig 5—Kidney Section through kidney cortex showing infiltration of large mononuclear cells around glomeruli and proximal convoluted tubules. Many of the cells are round the nuclei dense and the extoplasm sparse resembling large lymphocytes (X120).

Most of these granules were stained red, a few were blue. These areas of cellular infiltration corresponded with the nodules noted in the gross sections.

Suprarenals No abnormalities were noted

Pancreas Throughout the pancreas very many cells, similar to those seen in the kidneys, were noted. They invaded the parenchyma in Jurgi masses, so that only outlines of pancreatic icini could be recognized. Giemsa stain showed very few granules in the extoplasm of these cells.

Intestines Sections of the esophagus, stomach, and small intestines revealed, in the region of the submices, large accumulations of cells similar to those described in the kidness and panerers. In a few sections there was some necross which had hid to the formation of small ulcers. Very few polymorphonuclear lencocytes were found in these regions. The sections which were taken from the evaphagus showed many such ulcers. The blood ressels in these regions showed no changes.

Lymph nodes The architecture of the lymph nodes was preserved the sinusoida were distanted. The follich's were small and indistinctly visible Many large lymphocytic cells, poor in cytophasm were found. Given a stain revealed no granules within the cytophasm of these cells.

Skin nodules Sections which were taken from the skin nodules revealed mining necrotic tissue a moderate number of polymorphonuclear leucocytes, and a few large lymphocetic cells similar to those described before

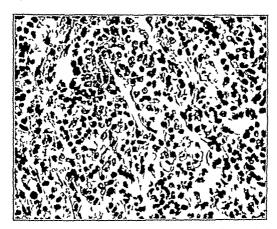


Fig. 6 -- Dura. Note the marked cellular infiltration. The cells resemble those in the kidneys. Variation in size shape, and staining quality can be seen. There are a few mitotic figures (X230)

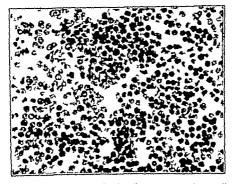


Fig. 7.—Section of bone marrow showing the presence of large cells, many resembling myelocytes. There is variation in size, shape and staining quality. The normal marrow spaces are absent. Note the mitotic figures in the upper central field (X503.)

Dura Sections of the dura showed cells similar to those previously described (Fig 6) The nuclear details were not recognizable and very little cytoplasm was present. Neither the Giemsa nor the oxydase stains revealed any granules. There were no mitotic figures. In only very few fields did the cells actually invade the deeper portions of the dura.

Brain Sections of the brain showed no abnormal changes

Bone marrow (tibia) In some of the fields the bone marrow showed cells similar to those described in the dura (Fig 7) The Giemsa and oxydase stains revealed a few granules within the cytoplasm. Other sections revealed cells which were larger than those described before, which showed a loose chromatin network of the nuclei, and many mitotic figures. The cells in general varied in size, shape, and staining quality, and appeared to infiltrate the bone marrow. In many portions large areas of necrosis were seen in which only ghosts of cells were recognizable. The Giemsa and oxydase stains revealed many neutrophilic, a few cosinophilic, and basophilic granules in the larger cells. Some of the sections revealed an invasion of the bone and periosteum by these cells. Sections which were taken from the bone marrow of the ribs and sternum showed a moderate number of fat cells in addition to occasional large cells similar to those described in the dura

# DISCUSSION

The clinical and pathologic diagnosis in this case presented many difficulties. The appearance of multiple tumors in the skull, proptosis, x-ray evidence of rarefaction and destruction in the membranous and long bones, marked anemia, severe emaciation and cachexia, suggested the possibility of generalized sarcomatosis (the primary focus unknown), chloroma, multiple myeloma, sympaticoblastoma of the Hutchinson type, generalized xanthomatosis (Christian's syndrome), lymphosarcoma, atypical leucemia, and leucosarcomatosis. Because this case offered so many diagnostic possibilities, and because the anatomic and histologic findings at autopsy were so unusual, it is felt that a detailed discussion of the differential diagnosis would be of value

Leucemia -Chinically I did not feel that this case was one of leuce-In infancy and childhood leucemia occurs most frequently in the acute form with a course resembling sepsis with extreme prostration and high fever, ulcerative and gangrenous lesions in the buccal mucosa, tonsils or pharynx, associated with enlargement of the lymph nodes and spleen, purpuric manifestations, and the presence of many immature lymphoid or myeloid cells in the peripheral blood Repeated examinations of the blood in this case failed to reveal many immature cells The superficial lymph nodes and the spleen were only slightly enlarged Diffuse destruction of bone as was found on x-ray examination is very unusual in leucemia Ewing2 states that "the spongy trabeculae are often absorbed and even the shafts may be thinned, but a distinctly aggressive destruction of bone as in true tumors is missing " Postmortem findings were not typical of leucemia lymph nodes did not show marked hyperplasia, the splenic follicles were atrophic, and the bone marrow consisted mainly of cells that

varied in size, shape, and staining quality, many of which revealed mitotic figures, rarely seen in leucemia, but common in neoplasms

Chloroma -This disease is essentially one of early childhood, and is characterized by the development of infiltrating tumor masses in the eranial bones, orbits paranasal sinuses, ribs, and sternum exophthalmos, progressive blindness, and deafness commonly occur The selera frequently have a peculiar greenish hue, unlike icterus The lymph nodes, liver, and spleen are frequently enlarged presence of tumor masses in the alimentary tract may produce severe intestinal symptoms The blood shows immature cells, either of the lymphoid or myeloid type usually with a moderate to marked leuco cytosis At autopsy tumor masses are found most commonly involving the periosteum, the dura, and the ligamentous structures. The tumor growths in a vast majority of cases are characteristically of arcenish color The bone marrow is red or gravish red, occasionally greenish Histologically, the tumor cells tend to form parallel rows, and appear as large undifferentiated nongranular mononuclear cells My case was not typical of chloroma From the blood findings one could not estab lish the presence of leucemia, a great many of the bone marrow cells exhibited malignant changes conforming to a true neoplasm. The morphologic appearance of the epidural tumor, however, easily could have suggested the diagnosis of chloroma even though it did not pre sent the characteristic green color

Multiple Myeloma -Multiple myeloma is an exceedingly rare disease in childhood . It is characterized by a diffuse involvement of the osseous system with predilection for the vertebra, sternum, ribs clavi cles, scapula, and ilium Paraplegia occurs in 40 per cent of the cases, indicating extensive disease of the vertebra. A pathologic fracture is frequently the first indication of bone disease occurring in 62 per cent of the cases and most commonly involving a rib 5 Marked in volvement of the skull may produce exophthalmos and symptoms of increased intracranial pressure Bence-Jones proteinuria is found in nearly 50 per cent of the cases Berkheiser' states that any marked change in the blood picture speaks against myeloma. X ray examina tion reveals multiple areas of medullary rarefaction with erosion of the cortex, in places presenting a definitely punched-out appearance Perforation is frequently observed Histologically, the tumors are composed of large cells often resembling plasma cells lying in a vascu lar, delicate connective tissue and stroma Chinically, I feel that it is possible to exclude multiple myeloma Several examinations failed to reveal Bence-Jones protein in the urine There were no pathologic fractures and x ray examination in my case revealed a diffuse rid dling of the bones involved unlike multiple myeloma in which the areas of rarefaction are usually isolated and sharply defined. The

epidural tumors and cellular infiltrations in the pancreas and kidneys found at autopsy are unusual in myeloma. Histologically, the tumor cells do not resemble the large plasma cell type usually found in myeloma.

Sympaticoblastoma -Sympaticoblastoma of the Hutchinson type is characterized in the majority of cases by swelling of the bones of the skull, exophthalmos, unilateral or bilateral with ecchymotic discoloration of the lids, profound secondary anemia without leucocytosis and the presence of an abdominal tumor in 50 per cent of the cases creased intracranial pressure with progressive blindness is common The tumors in the cranial bones increase rapidly in size filling up the temporal fossae, and proptosis becomes so marked that the cornea The superficial lymph nodes are moderately enlarged ulcerates X-ray examination reveals a diffuse mottling of the skull, periosteal thickening of the long bones, and small areas of destruction autopsy a primary tumor is found, usually in an adrenal gland tologically, the tumor is composed of cells and their processes, derived from embryonic sympathetic nervous tissue An abdominal tumor was not palpated in my case Postmortem examination obviously revealed that we were not dealing with a sympaticoblastoma

Lymphosarcoma - Lymphosarcoma occurs with greatest frequency between the ages of twenty and twenty-five years, and rarely in childhood 2 It arises in the retroperitoneal, mesenteric mediastinal, cervical, and superficial lymph nodes, and uncommonly in isolated nodes in the intestinal wall. Kundrate states that it is a regional disease of lymphoid tissue which spreads as a continuous growth through the lymph channels, thereby differing from the systemic character of leu-Isolated metastases in distant organs are rare, but in advanced cases the growth may invade the blood vessels, and true metastatic tumors form in the lungs, kidneys, skin, and other organs such instances atypical cells similar to those found in the tumor may also appear in the peripheral blood in large numbers, making the distinction between lymphosarcoma and leucemia difficult growth in the lymph nodes or lymphadenoid tissue could not be demonstrated in my case, the invasive and locally destructive characters of lymphosarcoma were absent in the organs involved, infiltration and accumulations of abnormal cells being the distinctive features anaplasia and mitosis of the cells were conspicuously absent in the lymph nodes described

Xanthomatosis (Christian's syndrome) —In 1919 Christian' described a clinical syndrome in children consisting of "Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus" He considered a disturbed pituitary function as the cause of the syndrome Rowlands in 1928 associated Christian's syndrome with generalized xanthomato-

sis, a disease primarily the result of disordered fat metabolism in which the reticulo-endothelial system shows an excessive storage of lipoids, frequently in the form of cholesterol. The disturbed pituitary function is due to the encroachment of pseudotumors upon the pitm tary body or tuber emercum Orbital involvement frequently causes exoplithalmos. The most outstanding clinical feature is the presence of defects in the skull characteristically involving the inner table of the skull more than the outer, having distinct, clear-cut but irregular edges and often presenting a maplike or geographical appearance (Schüller) There is a tendency of the disease to spontaneous remis sions and healing with new bone formation following x ray treatment to the affected areas 9 10 11 My patient showed no evidence of dis turbed pituitary function the course of the disease was progressive x ray examination of the skull did not reveal distinct, clear out areas with irregular edges and x ray treatment of the affected regions did not result in healing. Two examinations of the blood revealed normal cholesterol values and postmortem histologic examination did not reveal the typical lipoid laden xanthoma cells

Loucotarcomatosis.—In 1904 Sternberg<sup>13</sup> attempted to isolate from recognized cases of leucemia certain cases characterized by the presence in the blood of large mononuclear cells which he believed to be pathologic lymphoeytes arising from an original tumor and by means of true metastasis producing a generalized systemic disease. He applied the name leucosarcomatosis and called these cells "leucosarcoma cells" Anatomically this condition differed from typical leucemias in a more marked invasion into the lymphoid tissues particularly the mediastinum with tumor formations—a true blastomatous condition as opposed to a hyperplastic condition which he believed characteristic of the true leucemias. Within recent years the common belief is that the large mononuclear cells in the blood are myeloblasts or undifferentiated stem cells and that leucosarcomatoms is more closely related to myeloid than to lymphoid leucemia

In 3 of Sternberg's original 6 cases a sarcomatous tumor was found in the mediastinum. Two cases exhibited tumor formation on the inner surface of the dura and in the skull. The spleen was enlarged in 5 cases and there was generalized enlargement of the lymph nodes in 2 cases. In 1915, eleven years later Sternberg<sup>13</sup> reported a case of leucosarcomatosis which clinically resembles my case.

An eleven year-old child complained of fatigue and difficulty in breathing of five months' duration. Examination of the blood revenied a white blood count of 31,000 on admission and 5,250 shortly before death. Many large mononuclear cells "lence sarcoma cells' were observed at various times which led to the diagnosis of a probable lencosarcomatosis.

WBC 31,000 to 5,250, lymphocytes 4 to 28 per cent, polymorphonuclear leuco cytes 5 to 30 per cent, myelocytes 4 to 9 per cent, "leucosarcoma cells" 42 to 85 per cent.

Postmortem examination revealed large, flat, firm tumors on the inner surface of the dura, enlargement of the spleen, liver, mediastinal mesenteric and retroperitoneal lymph nodes some of which were fused by confluence. The tumors of the dura consisted histologically, of large mononuclear cells similar to those found in the blood. The cells invaded the dura. Similar cells were found in large numbers in some of the lymph nodes and invaded the surrounding fat tissue. They were also present in the splenic pulp, in the interlobular spaces of the liver, and in the bone marrow.

It is true that some of the large mononuclear cells that were observed in the blood of my case and classified as lymphocytes, might possibly have been "leucosarcoma cells" Sternberg describes the tumor cells as being similar to those found in the blood. It is also possible that the abnormal cells in my case were identical with those found in the epidural tumor. In Sternberg's case the tumors showed a marked predilection for the lymph nodes and lymphatic tissues, mine was conspicuous for the paucity of lymphatic tissue invasion.

Realizing that it is at least not a clear case of leucosarcomatosis, a further search of the literature was made in an attempt to classify my case. This search revealed only one case, similar enough to warrant my using the classification presented therein

In 1912, Buschke and Hirschfeld14 reported a case of a twenty-two year-old woman who, following a tuberculin injection, developed many tumor nodules throughout the skin The blood picture was normal until four days before death when the white blood count rose from 11.000 to 33,000 and many peculiar "tumor cells" appeared in the blood A puncture of the skin tumors revealed similar cells cells were large, the nuclei round, sometimes indented, and showed a dense chromatin network and often several nucleoli. The cytoplasm was stained sky-blue (Giemsa) In some of the cells azure granules could be found in varying numbers A differential count at that time revealed polymorphonuclear leucocytes 35 per cent, small lymphocytes 23 per cent, large lymphocytes 8 per cent, large mononuclear cells 5 per cent, and "tumor cells" 25 per cent Clinically, this was thought to be a form of leucemia consisting of abnormal cells classified by Pappenheim as "lymphoidocytes" The autopsy revealed in addition to a bilateral pulmonary tuberculosis, tumor nodules throughout the skin, some of which were the size of a walnut The eyes were somewhat bulging, the lids swollen The bones showed reddish grav The mucosa of the stomach presented tumor-like red tumor masses excrescences The large and small intestines showed ulcer-like depressions Both ovaries and parametria were invaded by tumors lymph nodes surrounding the abdominal aorta were enlarged, firm, and infiltrated by tumors When the scalp was removed, tumor nodules could be demonstrated throughout the frontal region. The dura also was covered by firm tumor nodules throughout. Smears taken from the various organs revealed cells which were identified as lymph oideevtes. In the lymph nodes many mast cells were found. Many mitotic figures could be demonstrated. The skin tumors showed large mononuclear cells similar to those found in the blood.

In discussing their case Buschke and Hirschfeld state that there is no question that it is one of sarcomatosis. The primary tumor could not be located with certainty They mention that in the literature there are eases of lymphosarcomatosis in which evidence of lymphatic leucemia is also present. They excluded this disease because they were unable to discover a new growth originating in the lymphatic In their own case the tumors in the lymph nodes and spleen were relatively insignificant and were most marked in the bone mar row, skin, and overies a pronounced deviation from the usual findings in lymphosarcoma They considered as a second possibility leuco-The lymphoidocytes they described were not similar sarcomatosis to Sternberg's "leucosarcoma cells", nevertheless, they were inclined to designate their case leucosarcomatosis in the sense that all leucemic proliferations, whether originating in mycloid or lymphatic hemato poletic organs, exhibiting a definite tendency toward an anatomically malignant growth of my cloid or lymphadenoid tissue should be called leucosarcomatosis. In summarizing their discussion they specify that theirs is the first case of leucosarcomatosis to be reported in which the new growth originated in the mycloid hematopoietic system and there fore proposed to classify it as one of myelosarcomatosis ' Several years later, Hirschfeld 18 in discussing this same case states that the lymphoidocytes described were of myeloid origin and the skin tumors consisted of dedifferentiated myeloid tissue

An analysis of my case brings out a striking similarity clinically and anatomically to Buschke and Hirschfald's case of myelosarcoma tosis. In both cases the white blood counts were only slightly elevated and the stained smears showed many atypical cells which resembled young lymphocytes. Hirschfald is recently of the opinion that they are dedifferentiated myeloid cells. My case also exhibited nodules throughout the skin, many of which had undergone abscess formation, however, at autopsy many mononuclear cells were present resembling those found in sections of tumor nodules in other organs. Similarly, tumors were present in the bones, gastrointestinal tract and in the dura mater, consisting of cells many of which were myeloid in character. Both cases were conspicuous for slight lymphatic involvement. In many places the malignant nature of the growths was made evident by the presence of mitotic figures and invasion of surrounding structures.

# SUMMARY

- 1 A case of an extremely rare disease in a child six and a half years old is presented in which the essential features are multiple malignant tumors throughout the skeletal system, gastrointestinal tract, kidneys, pancreas, and dura mater which histologically have the appearance of undifferentiated myeloid tissue The blood revealed many atypical cells that resembled young lymphocytes but may have been myeloid in origin
- 2 In an attempt to classify this case, a detailed clinical and pathologic differential diagnosis is presented
- 3 Emphasis is placed upon the difficulty in separating certain cases of leucemia from neoplastic disease
- 4 With a great deal of reservation I have classified this case myelosarcomatosis after Buschke and Hirschfeld

104 SOUTH MICHIGAN AVENUE.

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# HYPERTROPHIC PYLORIC STENOSIS IN TWINS

# ARTHUR F VARDEN M.D. SAN BERNARDING CALIF

ASCII 1 in discussing the chology of hypertrophic pyloric stenosis suggested the study of its occurrence in twins as a likely means of determining, at least in some cases, whether this condition is concenital He renorted a case in one of monozygotic twin girls and from this con cluded that it was probably not congenital. He suggested however, that a greater number of cases must be recorded before a definite opinion could be formed One must be very cautious in concluding that this is not hereditary but environmental as monogygotic twins might be hereditarily different, due to an unusual splitting of the ovum giving rise to great variability in the anlare. This view is not generally accepted, however Lasch's twins were physically identical and the placenta had but one corium. Single corium, while exceptional may also be found with dizygotic twinning though Lasch did not think the possibility of dizygotic twins applied to the case he reported patient died a few days after operation while the twin sister at no time showed symptoms or signs of pyloric stenosis

Recent studies of mental disorders in twins by Rosanoff\* should throw considerable light on the etiology of these conditions as regards heredity and environment. This method of clinical investigation also lends itself to the study of physical disorders and particularly pyloric stenosis as Lasch has pointed out.

The comparative rarity of this condition, together with the fact that obstetricians report that approximately one birth out of 80 is multiple makes the possible number of cases small. It is difficult to determine from some reports whether the twins are monozygotic or dizygotic. Wherever possible, this has been investigated by correspondence

All the reported cases discoverable were reviewed with the hope that interest would be created in reporting diseases occurring in monozygotic and dizygotic twins. In time a sufficient number may be recorded to make some conclusions possible on this and other conditions

Redalin mentioned pyloric stenosis in two sets of twins, but said nothing about the type of twinning so his cases cannot be used.

Davis, in 1924, reported pylone stenosis in twin boys, but un fortunately the records do not show whether the twins were monozygotic or dizygotic (Personal communication) The diagnosis was confirmed by operation and both patients made uneventful recoveries

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Moore's cases also occurred in monozygotic twin boys (Personal communication) They were not seen until the fourth week after onset, at which time their condition was precarious as well as complicated by malaria. Both presented typical signs and symptoms of pyloric stenosis, diagnosis being confirmed at operation. Due to their poor condition both died about a week after operation.

Bilderback's twins were monozygotic (personal communication), two months premature males Typical tumors were found at operation One twin died while the other made an uneventful recovery

Moniad<sup>6</sup> reported 228 cases of hypertrophic pyloric stenosis of which three cases were in three pairs of twins. The type of twinning was not mentioned but since they were normal one would suspect them to be dizygotic even though Lasch did not find it so in his cases.

Because of the discussion as to identification of monozygotic twins, the following criteria were used to establish this in our cases

- (1) Both were males, identical in every way by physical examination except one was more emaciated due to earlier onset of symptoms.
- (2) Hand prints were taken and found sufficiently alike to be classified as "1 Absolute Ab 1" according to Reichle  $^{\tau}$
- (3) For additional proof the obstetrician's note at time of delivery is quoted "The placenta was a large one in size although it was not weighed. Each cord was inserted at opposite sides of the placenta, each one having a battledore attachment. There was only one chorion present. The amnion separated two amniotic sacs. No line suggestive of a fusion of two placentas could be found. It was apparently composed of only one placenta, and in every way appeared normal."

# CASE REPORTS

CASE 1-History-T K, aged nine weeks, was admitted to the University of California Hospital, February 9, 1931, with the chief complaint of vomiting since one month of age Family history was significant as mother had arrested pul monary tuberculosis and the twin brother had also been vomiting although not so much Delivery had been by low forceps, birth weight 6 pounds, with question of prematurity No breast milk was available and he was given whole cow's milk, boiled, diluted with water After a week this was changed to Dryco upon which he did well for three weeks then started vomiting Formula was again changed to lactic acid milk, next to diluted evaporated milk and later to Eagle Brand milk without improvement. For one week before entry he was given atropine 1/1000 to 1/600 grain before feedings The vomiting continued, occurring shortly after feedings and at times was projectile. For two days previous to admission the vomitus contained material resembling coffee grounds and he vomited water as well as milk Intramuscular blood (15 cc) was given Marked constitution had been noted for two weeks although enemis showed some return. There had been no infection.

Weight on admission was 3170 grams and patient was markedly dehydrated, emaciated and pale having the typical appearance of a "little old man" with very thin cheeks and simken fontanel. He seemed very hungry and sucked his fists con

stantly Skin was pale, dry and inelastic and there were small shotty glands in the cervical and axillary regions. Chest was poorly clothed but otherwise negative Abdomen was scaphold, thin and a small firm tunner mass could be felt in the right upper quadrant. No peristaltic waves could be made out at any time

Laboratory Data.—Blood on admission was Hemoglobin 82 per cent (8ahli) R B C 6,110 000 W.B C 18,500 Piff Poirs 52 Lymphorytes 45 Mononuclear 1 Basophiles 1, Myclocytes 1 Blood hemistry 1 lasma CO = 04.3 rolumes per cent, Plasma Ci = 470 mg per 100 cc. N 1.5 = 2/3 mg per 100 cc. Wasser mann and Taberculin 0 1 were both negative.

Barium meal with fluoroscopy showed 80 per cent gastric retention at the end of 0 hours. Bronchopneumonia was revealed in the permanent films made



Fig. 1 -T L. left D. R. right. Aged twenty-one months.

Treatment —Patient was given parenteral fluids and thickened feedings preceded by phonobarbital 0 004 gram. Projectile vomiting of water and formula continued and gastric lavage consistently showed marked retention of food in the stomach

After further preparation with parenteral fluids a Rammstedt operation was done on February 10 1982. A typical pyloric tumor was found Just before closing the abdomen the peritoneal eavity was filled with normal soline.

After operation, the infant retained the first few small feedings of whole lactic neid milk with added Kare sugar but then began to vomit. Vomitus contained old blood. His temperature was 38 6 C He coughed occasionally but his chest was negative to physical examination. He continued to vomit most of his feedings and the amount of blood increased so that the second postoperative day he ap-

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blood and a markedly positive benzidine t at for blood was also noted in the few stools passed. Gastrle lavage twice daily consistently showed considerable retention, February 13, a Rummstedt operation was done under local anesthesia and a typical olive-shaped tumor was found. A small section taken for examination revealed hyper trophy, hyperplasia, interstitial edema and hyalinization of pyloric smooth muscle. Just before closure of the wound the abdomen was filled with normal saline. His postoperative course was uneventful. He took gradually increasing amounts of formula without comiting and his weight steadily increased. His stools later became negative for blood. He was transfused to improve his anemia but as in the case of his brother this was difficult because of an apparent anomaly in the valves of his science.

Patient was discharged 1. days after operation weighing 4380 grams, a gain of 190 grams since admission and continued to do well.

Both patients were seen again in September 1932, aged 21 months. They had been perfectly well since discharge T K weighed 31 pounds 10 ounces and was 34¼ inches tall, while D K is weight was 30 pounds 7 ounces and his height 34½ inches. T K has been five months behind his twin in development, that is, walking, talking, etc

### CONCLUSIONS

- 1 Hypertroplus pyloric stenosis is reported in monozygotic twin boys. A review of previous reports shows that accurate information regarding monozygotic or dizygotic twinning is seldom mentioned, decreasing the value of these reports. Reports of pyloric stenosis occurring in only one of twins should likewise be carefully reported regarding placentation.
- 2 Hypertrophic pyloric stenosis in twins is rare and in the small number collected one would conclude that there is more evidence in favor of a congenital theory than against it but one must await the recording of more cases before a real conclusion can be made.

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peared very pale and decidedly worse. His hemoglobin was 34 per cent (S) R.B.C 1,780,000. He was given 75 c.c citrated blood with great difficulty, presumably due to an anomaly of the valves in his veins. Following this transfusion he im proved generally, vomited less but his stools became dark and tarry. His hemoglobin was 42 per cent (S) and R.B.C. 2,480,000

Two days later he was transfused again with the same difficulty Parenteral fluids were administered as needed. After a third transfusion his hemoglobin went up to 65 per cent (S) and his RBC were 3,700,000

After five days vomiting ceased and the small amounts he spit up did not con tain blood although his stools continued to be tarry for a few days longer and a positive Benzidine test was obtained for a still longer period, but finally the stools became normal He gained slowly and additional transfusions were necessary

On April 6 he had fever and signs of bronchopneumonia were present, most marked on the right. This was confirmed by roentgenogram. The following day the left ear drum was incised and drained pus for a few days. His cough and a low grade fever persisted. Chest films remained unchanged and suggested perifocal tuberculosis. Tuberculin test 10 mg which was repeated, was negative

Since his weight had become stationary the formula was changed to two parts evaporated milk to one part of stock solution, following which he gained steadily in spite of occasional vomiting

On March 26 he developed definite signs of whooping cough after an accidental exposure some days before. He became extremely ill, cyanotic and toxic and vomited constantly. He was given pertussis vaccine without demonstrable improvement. He improved when placed in an oxygen tent but became cyanotic whenever removed for feedings. After a very stormy course he was discharged from the hospital on June 29, 1931, still having a slight cough but afebrile and otherwise in good condition. Discharge weight 5800 grams

CASE 2 - History -D K., white male, aged nine weeks, was admitted to the University of California Hospital on February 10, 1931, with the same complaint as his brother, who had been admitted the previous day, vomiting since one month Birth and feeding history were practically the same as of age only less severe He did well for a month when he began to vomit a small that of twin brother This usually occurred immediately after feeding, never longer amount of formula than one half hour Vomiting was projectile in type and did not show mucus, blood Vomiting continued intermittently for two weeks during which he lost most of his feedings, so the formula was changed to evaporated milk 61/2 ounces, water 14 ounces, 4 ounces every four hours, with cessation of vomiting until two During this final period he vomited practically everything days before admission including water He had gained 3 ounces since birth but failed considerably during Stools had been few and constipated and there had been no the past three weeks infection or fever

Physical examination on admission revealed a well developed but poorly nourished dehydrated infant, weighing 3800 grams. His skin was inelastic, dry and pale. He had a soft scaphoid abdomen, and a definite small firm mass could be felt in the left upper quadrant but no peristaltic wave could be made out.

Laboratory Data—Hemoglobin 63 7 per cent (S), RBC 3,150,000, WBC 10,900, Polvs 32 per cent Tuberculin negative Plasma CO, 43 7 volume per cent. Barium meal under fluoroscopy showed marked retention

Treatment —For three days following admission whole lactic acid milk with 10 per cent added Karo thickened with rice flour, was given every four hours with phenobarbital 0 004 twenty minutes before each feeding Additional fluids were administered parenterally Vomiting continued and soon became dark red with

set far apart with their horizontal axes directed laterally and strabis mus is often present. While the height and circumference are usually normal, the skull length is shortened and the occiput flat, giving a brachy cephalic type.

Physical development may be normal or retarded. Mental deficiency may or may not be present and other deformities may be found, such as syndactvium, high palate undescended testes, and acrocyanosis

X ray of the skull shows the wide separation of the orbits and large anterior nares. Intersutural bones may be present or the sutures in complete with absence of digitations







Fig. ..- Case 2.

According to Reilly, the most common form is that with facies and a family tendency our cases falling into this variety

We are describing briefly two cases, a female twelve years of age and a male of six years brother and sister. The mother of these chil dren, aged forty years has the typical hyperteloric facies more marked than the daughter or son. She appeared very sensitive about her condition and would not consent to allow us a picture of herself, although she showed us a picture taken in her infancy which illustrates the facies quite well. On further question it was found that her father also had a similar appearance. As near as we could determine the mentality of both adults was apparently normal. A third child, the oldest in the family is the only normal one.

### CASE REPORTS

Case 1 -Ed D, male, six years of age, was brought to the physician because of frequent sore throat and head colds

The history of birth and development appeared entirely normal, and his general health was excellent

On casual inspection, attention was immediately drawn to the eyes which appeared to be wide spread, and the mother volunteered that the boy had been that way since birth and that her second child, a girl, had the same type of face

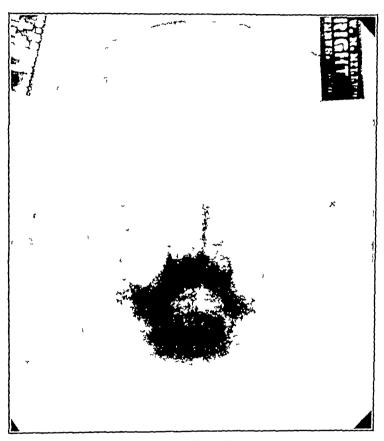


Fig 3 --- Case 2

The essential findings are in the face and head. The skull seemed unusually large, particularly in width, the occiput rather flat, the forehead high, while the frontal and orbital prominences were very slight. It would seem that the skull has been flattened from before backward

The other notable feature was the appearance of the eyes, seemingly far apart. The bridge of the nose was moderately depressed and broad, the nose not being retroussé

The eyegrounds were normal and no definite strabismus was noted. The hard palate seemed high and the child spoke with a mild defect in articulation.

Physically and mentally, the child appeared to be normal in all other respects Tuberculin and Wassermann tests were both negative While this child is a mild case and the pleture is not particularly convincing the factes was characteristic on actual inspection and served to discover the more definite case in the sister and also bring to light the definite familial history in the parent and grandparent Nray of the skull was not unusual

CASE 2.-Em D., a sister twelve years of age, presented a more definite factes than her brother

Her birth developmental and past medical histories were all quite normal. Si appeared unusually alert and intelligent and was quite sensitive about her face

The eyes were unusually far apart. The bridge of the nose was greatly depressed and broadened while the nose was retroused. The face seemed small in comparison to the cranium.

There were no other abnormal physical findings

Table I gives measurements in millimeters of patients and comparison with normal subjects of the same ages

TABLE I

ORBIT	FD D TATIENT	G 1 R. VORMAL	EM D PATIENT	1_ TR NORMAL	
Between internal canthi	35 mm	30 mm	40 mm	24 mm	
Between external canthi	100 mm.	85 mm.	105 mm.	90 mm	
Between center of pupils	60 mm		0 mm	_	
Right orbital beight	30 mm	_2 mm	28 mm	23 mm	
Left orbital height	30 mm	22 mm.	28 mm	25 mm	
Right orbital width	40 mm.	30 mm	45 mni	35 mm.	
Left orbital width	40 mm	30 mm.	45 mm.	35 mm	
8KULL.					
Greatest circumference	415 mm	700 mm	543 mm	52. mm	
Greatest length	170 mm	170 mm	170 mm	170 mm	
Greatest width	140 mm	130 mm	160 mm.	140 mm	
Cephalic index	83 mm	76 mm	04 1 mm	80 mm	

<sup>(</sup>The cephalic index is obtained by multiplying the cranial breaith by 100 and dividing by the cranial length.)

The following is the radiologic diagnosis of the x-ray of Em D  $\,$  (Dr W II. Miller)

Shull Yray examination of the skull made in the lateral and anteroposterior views shows an overgrowth of the lesser wings of the sphenoids which have essified early and grow excessively. The orbits are widely separated due to the overgrowth of the wings of the sphenoids. The anterior portion of the skull is irregular in out lines suture lines are normal.

Teeth Normal.

Sixuses Normal

Sella Turcica Blightly enlarged.

#### BUMMARY

Two cases of hypertelorism with a definite familial history, all with out mental deficiency are reported

350 E. STATE STREET

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in the first few days. These began to disappear and by the time the temperature was normal he was symptom free, except for an occasional sweat There was no change in his weight during his hospitalization He was discharged symptom free after two weeks' stay in the hospital and at the end of three months is apparently well The duration of symptoms was eleven weeks

Epidemiologic Study -After the confirmatory evidence afforded by laboratory work, we attempted to investigate the milk supply. The milk was obtained from a special herd which gave no history of abortions. The milk was not pasteurized and the dairyman had forgotten to tell the mother to boil the milk, as was his custom when babies were started on this brand The milk was not labeled as pasteurized Blood studies in this herd revealed a number of positive and suspicious reactors

#### SUMMARY

- 1 A case of B abortus infection, beginning in a seven-months old infant is reported
- 2 This is the first case to our knowledge that has been reported from this section of the country in infancy or childhood
- 3 A clinical diagnosis was made and was verified by positive blood culture and agglutination test
- 4 B abortus infection in infancy may be more frequent than is now Any unexplained fever should suggest the possibility of recognized its occurrence
- 5 Universal use of pasteurized milk will eliminate this disease in the early years of life

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#### ALLFRGIC EPILEPSY

### J KLEIN M D CHICAGO ILLINOIS

Diopartific epilepsy is a clinical syndrome which is as yet not clearly understood. The observation of an asthmatic clild suffering from epileptic seizures brought up the question of allergy in relation to epilepsy. Spangler' studied 100 consecutive cases of adult epilepsy and found that in 88 per cent there was a history of allergy in the ancestors. He notes that gastrointestinal allergy is an important factor in the development of convulsions in the epileptic child. In his series Spangler reported that 32 per cent of the patients had convulsions in infancy. Among the parents and grandparents he found 11 cases of epilepsy, 35 cases of asthma, 7 of hay fever, 14 with urticaria 6 with a history of cezema, and 6 who had migraine. Multiple allergic mainfestations were observed in one third of all the epileptic patients.

A II Rowe<sup>2</sup> states that allergy is undoubtedly the cause of certain cases of epilepsy especially in children. He reports two such cases (1) a four year old asthmatic child who was sensitive to pollens and in whom immunization resulted in freedom from asthma and cure of the epilepsy, and (2) an eleven year-old child who suffered from petit malfor six years and was sensitive to cat horse, and rabbit hair. De sensitization to horse hair and removal of her hair mattress resulted in complete relief for two years. S. J. Levin<sup>2</sup> reported a three-year-old child with epileptic seizures in association with sensitization to American, Swiss and Roquefort cheese. On eliminating cheese from the diet there was a complete cessation of epileptic reactions. Levin gives credit to Pagniez and Lieutaud<sup>4</sup> for having first pointed out the frequent occurrence of allergic manifestations in certain instances of epilepsy. Their first report was that of a young man who suffered from epileptic seizures which were induced by eating chocolate.

In this country J L Miller' was among the first to emphasize the importance of allergy in relation to the epileptic syndrome. He expresses the opinion that the epileptic seizure is an anaphylactic manifestation, and thinks that in some cases of epilepsy food sensitization is responsible.

Angiospasm is an important factor in the explanation of epileptic manifestations and is regarded by some as one of the effects of al lergy. There are a number of authorities who explain the epileptic syndrome on the basis of a cortical ischemia induced by angiospasm (Perez, Olkan, Bolsi, Etienne)

Back of these allergic and epileptic manifestations there is some hereditary defect which is transmitted by the germ plasm. Thus Frugonic has proved that the allergic constitution is transmissible through either parent, although the type of manifestations may differ in parent and child

As to the nature of this metabolic or constitutional defect, little is definitely known. However, Auguste Lumiere in 1921 published a brilliant hypothesis in his study on the rôle of colloids in biology. This work deserves to receive more attention since it is based on experimental evidence and seems of great practical importance. Lumiere maintains that anaphylactic phenomena are due to an alteration in the colloids of the tissue fluids and blood plasma wherein the usually finely dispersed colloid particles are agglutinated and form precipitates in the perivascular lymphatics and tissue spaces. A flocculation of these altered colloid particles in the lungs causes asthmatic symptoms, in the brain it results in epilepsy. Lumiere went further and suggested that treatment should aim at dissolving or breaking up this abnormal state of the colloids. Lumiere's theories and experiments are deserving of more intensive investigation.

Because of its implications and clinical interest I wish to add the following clinical record to the literature

L B, aged eight years, first attended the Pediatric Department at Northwestern University on March 21, 1931. She complained of frequent attacks of dyspnea, which had been occurring at irregular intervals since the age of six months. She also coughed frequently, and was 10 per cent under weight. L B was the first born child and had been breast fed. As an infant she was very fat. At one month of age the patient developed eczema which persisted until she was two years old, and has never recurred. The periods of asthmatic dyspnea appear every few days and at times are so severe that she becomes cyanotic

She had measles, whooping cough, hay fever, and later pneumonia complicated by empyema (aged six years). Tonsillectomy and adenoidectomy were performed at four years of age. The family history was not very illuminating. The mother had died of pneumonia and heart trouble at twenty eight years of age. The father is living and well. No history of familial asthma, hav fever, hives, or epilepsy could be elicited from an aunt who accompanied the child.

On Jan. 28, 1930, the patient had an attack of epileptic convulsions. The attack was preceded by a severe paroxysm of asthma and followed by cyanosis and coma Since then the patient has been troubled by epileptic convulsions, which occur every week, sometimes several times weekly. It was found that the number of attacks was reduced by the asthmatic treatment. When the latter was omitted for a period of four months, the epileptic seizures increased in frequency.

On physical examination the patient was found to be of asthenic habitus and very much undernourished. Her cheeks were flushed The respirations were fre quent and labored

Examination of the head and neck showed no noteworthy defects. The eyes reacted to light and accommodation. The ears were normal, as was the hearing. The teeth were apparently normal. The tonsils had been removed. The tongue in its anterior half presented enlarged, congested papillae which gave it a "raspberry" appearance.

The thorax was barrel shaped and the sternum was unusually prominent. There was very little motion of the cliest on respiration. The lungs were hyperresonant and emphysematous. The breath sounds were distant. Numerous fine and coarse piping raises were heard on expiration.

The heart borders were indistinct because of the emphysema. The apex was in the fifth interspace and in the mid clavicular line. The heart tones were muffled. There were no murmurs.

The abdomen was retracted Ao localized rigidity or tenderness was elicited nor were there any palpable masses. Acuter the liver nor the spleen was palpable

The skin over the left forcarm on the extensor surface persented a dry, crythem atous area which had been present for months and looked like an exematous lesion.

The extremities were normal. There were no other noteworthy findings in the

Blood Hemoglobin 75 per cent R B C 0,180,000; W B C 21 450 Differential Count Polymorphonucleurs 63 per cent, lymphocytes 31 per cent cosinophiles 5 per cent

Urine Straw color ap gr 1024 cloudy, reaction alkalina, few white blood corpuseles, amorphous phosphates, trace of albumin no sugar or discette acid.

X ray Examination The frontal sinuses were not developed. The ethnoids were not acrated. The maxillary antra were small and not well acrated. The right maxillary antrum was denser than the left. The sphenoid sinuses were not yet acrated. The sella turcica was normal.

The elect reentgenogram revealed a normal cardiac and aertic outline. The cardiophrenic angle was especially prominent on the right side because of the low disphraym.

Skin Tests These tests were done in the Allergy Clinic and showed that the child was sensitive to chicken feathers, duck feathers horse dander, house dust, eggs radish rhubarb spinach, tomate mustard, herring ragweed (++++) and cockleburr

Spatum Examination There were no tubercle bacilli. There were numerous gram positive diplococci bacilli, and short chain streptococci. Eosinophiles were present, but no Currenmann s spirals or crystals

Olinical Diagnosis Asthma and epilepsy

routine physical examination

#### COMMENT

This eight year-old girl is of a markedly allergic constitution (ec zema, hay fever, asthma, skin tests) and, in addition, suffers from frequent epileptic seizures, which seem to be related in their incidence to the attacks of asthma. It is possible that these convulsive disturb ances may be due to an alkalosis brought about by asphyxia during the asthmatic paroxysm. However it is quite possible that both the asthmatic and the epileptic symptoms may be due to the underlying allergic reaction.

The treatment has included calcium ephedrin belladonna, and at tempts at desensitization against offending allergens. At times symptomatic relief is afforded but in general, the results of treatment thus far have not been very encouraging. Lately the use of sodium thiosulphate has been resorted to with the purpose of altering the colloid state. This treatment was suggested by Lumiere and is based on

his experimental studies. For the past three months there have been no epileptic seizures and two mild attacks of asthma However, it is too soon to make any critical comments on the thiosulphate therapy

### SUMMARY

- 1 Attention is called to the very significant relation of the state of allergy to certain types of "idiopathic epilepsy"
- 2 A case report is presented of an allergic eight-year-old girl who has epileptic seizures in association with her asthma

3836 W ADAMS STREET

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# THE USE OF WHOLE CITRATED BLOOD INTRAMUSCULARLY IN A MLASLES EPIDEMIC

### ROBERT M LORD, M.D PROVIDENCE, R I

In January and February of 1932 there occurred in Providence, R. I., a widespread epidemic of measles. The epidemic was a mild form of the disease, and did not tend to cause complications. The available supply of convolescent serum was soon exhausted and the paucity of adult cases during the epidemic prevented a replacement of the supply. Physicians were therefore unable to obtain serum for use on the younger children exposed to this disease, and in a number of cities and towns were forted to use blood acquired from the convolescent cases in the homes, or in a few instances from parents who had the disease either in childhood or in youth

The total number of cases in January and February, 1932, reported to the Providence Board of Health was 4,827, with only 10 deaths during these months. I wish to report 89 cases which were given whole citrated blood direct from the donor to the recipient in the homes. The method of administration was to draw 3 c c of sterile 2 per cent sodium citrate solution into a 30 c c syringe and withdraw from one of the veius in the donor's arm anywhere from 5 to 25 c.c. of whole blood. This was injected intramuscularly into the external aspect of the left thigh of the recipient about midway between the great trochanter and the external condyle of the femure.

The average time of injection was four days after the rash occurred in the patient to whom the child was exposed. The average amount injected was 20 c c. The majority of the donors were brothers or sisters recovering from measles and the blood was not taken unless the donor's temperature had been below 100° F for forty-eight hours and no complications were present. In 14 cases 25 to 30 c c of the parent s blood who had had measles from ten to thirty five years previously was used. The age of the recipients varied from four months to eleven years. After the blood was given the parents were instructed not to carry out any precautions as to isolation except in four in stances where the blood was given to infants under one year old.

I have apparated these 89 cases into 4 different groups because they consist of the observations of 4 different pediatricians. All of the recipients in Groups 1 and 2 were exposed to other members of their own families, only one patient being exposed to a schoolmate and in this case the recipient showed definite signs of measles. In this way

it is possible to evaluate the severity of the cases treated with whole blood as compared with the untreated cases in these families. I realize that this evaluation of necessity must be a matter of personal judgment and may be open to criticism.

The first group of 29 cases are from my own practice and were under my personal observation. I have classified the average case not treated with whole blood during this epidemic in the following wav temperature 102°-104° F, conjunctivitis 3-plus, rash 3-plus, cough 3-plus, and duration four days. The cases which were treated with whole citrated blood are shown in Table I

TABLE I

**************************************									
NAME	HIGHEST TEMP	CONJUNCTIVITIS	RASH	COLGII	DURATION IN DAYS	COMPLICATION			
AH	101	0	+	0	2	0			
D W	103	0	++	+	2	0			
s $L$	101	+	+	0	1	0			
Dр	103	+	+	+	2	0			
R. K	101	0	+	0	2 1 2	0			
CK	102	+	++	+	2	0			
${f L}$	100	0	+	0	1	0			
A C	100	0	+	0	1 2 2 3	0			
EC	100	0	+	0	2	0			
J C	105	++	+++	++	3	0			
ВC	100	0	++	0	2	0			
DG	High	0	++	0	1 1 1	0			
N O'N	105	+	++	+	1	) 0			
NF	100	0	+	0	1	0			
BG	101	+	+++	0	1	0			
DG	High	+++	+++	+++	4	0			
PD	101	0	++	+	2	0			
CO	99 6	0	+	0	1	0			
TH	101	0	+++	0	2	0			
A C	986	+	++	0	1	0			
R C	9	0	++	+	1	0			
$\mathbf{E} \mathbf{K}$	99 6	0	++	0	1 1	0			
RK	996	0	++	0		0			
RV	99 6	0	++	0	1	0			
vs	99 6	0	++	0	1	0			
J W	101 6	0	+	+	2	0			
wк	102	+	++	++	2	0			
CK	102	+ [	++	++	1 2 2 2 2	0			
СM	102	0	+	+	2	0			

The second group, 38 in number, are tabulated from the records of my associates and from the observation of the parents, asking them to compare the donor and the recipient as to comparative severity of the measles. In every instance the donor was older than the recipient and would be expected to have a milder case than the recipient. The terms used in this group are as follows "Mild" means slight conjunctivities, slight cough, temperature not over 102° F and a generalized rash "Severe" means a typical case of photophobia and conjunctivities, irritative constant cough, temperature 102° to 104° F, generalized confluent rash. There were 24 mild cases and 6 severe cases

Of the latter 3 patients had received but 5 cc to 10 cc of whole citrated blood. Eight cases did not contract measles at all but were exposed thoroughly and no precautionary isolation was attempted

The third group consists of 17 cases in an orphanage. One of my associates took 8 ounces of citrated blood from one donor, a girl who had had measles within eight weeks and gave about 10 cc to 15 cc to each of the children. These children had been exposed twice in a nursery. The first exposure and the second exposure were about eighteen days apart. None of these children had had measles. They varied in ago from eighteen months to four years. Ten developed very light cases while 7 did not have measles at all.

In a fourth group I wish to give in more detail a summary of the manifestations of measles which occurred in 5 cases, because in this way some of the points which I wish to emphasize in the use of whole citrated blood as a therapeutic measure of great value in lessening the severity and preventing the complications of measles can be pointed out

Case 1—Earl M, a twin cleven years old developed measles rash Dec. 25 1931
Temperature 101 to 102 F marked photophobia and conjunctivitis severe con
flour days but coughed for one week On Dec 29 when his temperature was 98,
20 c.c. of whole blood was taken from him and injected into the left thigh of
Florence M, a twin sister On Jan 5 1932, Florence started with a slight cough
and temperature 101 to 102 On Jan 0 she had a generalized severe confluent
measles rash all over her body which appeared within twelve hours. Temperature
101 F On Jan 7 there was a sudden drop in temperature to 90 during the
night and the cough disappeared in forty-eight hours.

This case indicates I think, that even in older children whole blood may influence measles to a marked degree.

CASE 2—Barbara W three and a half years old, was exposed to Marshall W on Jan 7, 1932 Marshall W had a temperature of 101 to 105 F, with severe conjunctivitis moderate cough, marked rush and no signs in the lungs. On Jan 10 when his temperature was 98.8 20 a.c. of whole blood was taken and injected into the left thigh of Barbara W On Jan 16 ten days after the brother s rush and six days after the injection of the blood Barbara W began limping and complaining bitterly of pain in the left leg On physical examination she was very tender over the outer aspect of the left thigh and passive or active movement of the leg was impossible. The temperature was 101 F There was no bone thickening On Jan 19, she was less tender, and on Jan 20 a faint typical measles rush came out all over the body The temperature came down to normal and the leg was much better as soon as the rush came out. There was no conjunctivitis photophobia, or cough.

This case was interesting in that the symptoms referable to the leg were severe and were undoubtedly a reaction to the denor's blood localized to the region of in jection and were very likely due to the onset of the disease itself which the serum of the whole blood succeeded in aborting

Case 8—Chester W, aged five years, the brother of Thomas W had a typical measles rash with bad cough and conjunctivitis on Jan. 21, 1932 An attempt was made to take blood from him on Jan. 25 This was unsuccessful and so 25 e.e. of

whole blood was taken from the mother, who had had measles about twenty years previously. This blood was injected in the left thigh of Thomas W. On Jan 31, ten days after his brother's rash and six days after the injection of the whole blood, he had severe pain in his left leg and was unable to move it. A typical measles rash broke out on Feb 1 with temperature of 101° to 103° F. On appear ance of the rash the pain in the leg disappeared. There was no conjunctivitis, very slight cough, and within twenty four hours the rash faded and the temperature dropped to 100°

This case illustrates the use of whole citrated blood from the parent with a similar local reaction to that which occurred in Case 2, where recent convalescent blood was used.

CASE 4—Sally L, five years old, was exposed in school to the child who sat next to her on Jan. 16, 1932. The schoolmate had a moderately severe case of measles with temperature 102° to 104°, she was sick four days, threatened with otitis media and had a cough persisting for one week. On Jan 23, seven days after exposure, Sally L was given 25 c.c of paternal blood in the left thigh. The father had had measles twenty eight years previously. On Jan 30, Sally L had a temperature of 101°. On Jan. 31, she had a faint generalized measles rash and a temperature of 100°, the next day the patient was well.

In this particular case the measles was influenced to a very marked degree. The father is a pediatrician and whether the potency of his blood was due to constant exposure to the virus of measles is an interesting question

Case 5—R. E G, Jr, aged two and a half years On Jan 30, 1931, R E G's sister had a typical measles which ran a mild course. Two days later 20 cc of whole blood taken from the father, who had had measles twenty two years ago when twenty years of age, was injected in the thigh. No attempt was made to isolate this child and he ran in and out of his sister's room, sometimes actually crawling over her bed. Ten days after administration of the whole blood he developed a temperature of 104° F. "Vomited, had pain in the left leg, was unable to move it. The next morning he was perfectly well, except that he had a blotchy rash all over the left leg." Two weeks after the first case an older brother and sister who had not had any blood injected, developed severe measles which lasted for eight days, with a temperature of 101° to 104° F. The brother, thirteen years of age, had a definite citis media in one car which was incised and drained for one week. No attempt at isolation was made from these two cases and R. E. G. was exposed constantly to his brother and sister. He never developed any other symptoms of measles than those mentioned after the first exposure.

This case speaks for itself—It is difficult to believe that there are any two year old children who are inherently immune to measles and this would be the only explanation possible unless the father's blood had conferred upon him a partial immunity

I therefore believe that it is very worth while to use whole citrated blood in the manner which I have described in this article to protect children from three months to six years of age from the complications which are very liable to follow measles. I do not believe in giving whole blood until three to four days after the rash appears in the case to which the child has been exposed, because if done earlier than this it may prevent any signs of measles, and the immunity thus conferred will last only a short time. There is also a psychologic ad-

vantage of using blood obtained from the patient's own family instead of the scrum supplied by the health department coming as the scrum does from unknown donors. It is probable that the attenuated measles which occurs may protect these children for life, or at least carry them through the years in which they might develop complications of a more or less scrious nature.

I wish to express my appreciation to Dr Henry E. Utter Dr William P Bustum, and Dr Reuben C. Bates for allowing me to use their cases in this article.

122 WATERMAN STREET

### ANTIQUES OF PEDIATRIC INTEREST

### T G H DRAKE, MB, FRCP(C)

THE ceremony of touching for scrofula, the King's Evil, was performed in England from the time of Edward I until the end of Queen Anne's reign (with the exception of during the reign of William and Mary), a period of nearly 700 years

In the reign of Henry VII, the presentation of a piece of gold was first generally introduced. This was the angel noble, a circulating gold coin of the time, on which an angel is represented standing with both feet on a dragon. A warrant issued in the reign of James I for the special coining of angels as touch pieces shows that although they were current coin, they were also made ready pieced for the purpose of suspension about the sufferer's neck during the ceremony of touch





Gold touch piece, Charles II, circa 1662 (diameter 7sths inch)

ing From the days of Charles II to those of Queen Anne, this gold coin being no longer current, a special gold medalet of the type illustrated, varying only in size and the name of the reigning sovereign, was struck and perforated for the ceremony

The immense popularity of the ceremony is shown by the entry in *Evelyn's Diary* for March 28, 1684 "There was so great a concourse of people with their children to be touch'd for the evil, that six or seven were crush'd to death by pressing at the chiruigeon's doore for tickets"

The following is Evelyn's description of the ceremony

"6 July, 1660 His majestie began first to touch for ye evil, according to custom thus his majestie sitting under his state in ye banquetting house, the chirurgeons cause the sick to be brought or led up

From the Department of Pediatrics University of Toronto and the Hospital for Sick Children Toronto

to the throne, where they kneeling, ye king strokes their faces or cheekes with both his hands at once at which instant a chaplaine in his formalities says. He put his hands upon them and he healed them. This is said to every one in particulat. When they have ben all touch d they come up againe in the same order, and the other chap laine kneeling, and having angel gold strung on white ribbon on his arme, delivers them one by one to his majestic who puts them about the neeks of the touch'd as they passe, whist the first chaplaine repeats, 'This is we true light who came into we world.'

The register of those touched for the King's Evil by Charles II extends from May, 1662 to April, 1682 and gives the number of persons touched by the king for the evil as 92 107, as many as 600 being touched at one ceremony

Belief in the efficacy of the royal touch for the cure of scrofula was not confined to the ignorant Richard Wiseman in Severall Chirurgicall Treatises, 1676, writes

"But it is not my business to enter into divinity controversies, all that I pretend to is first the attestation of the miracles and secondly, a direction for such as have not opportunity of receiving the benefit of that stupendous power"

And the following is his answer to those who questioned the miraculous cure

'For since it cannot be denied that many go away cured some will impute it onely to the journey they take, and the change of air, others to the effects of imagination and others to the wearing of gold

"The first of these is easily confuted by the hundreds of instances that are to be given of inhabitants of this city who certainly could meet with little change of air, or indeed of exercise, in a journey to White hall. The second is readily taken off by the examples of in fants, who have been frequently healed, though they have not been old enough to imagine any thing of the majesty, or other secret rays of divinity, that do attend kings, or do any other act that way to con tribute to the cure. The third hath more of colour in it because many that have been touched, have upon loss of their gold felt returns of their malady, which upon recovery of that have vanished. But in this case also we have many evidences of the contrary

"For his Majesty's royall father in his great extremity of Poverty had not gold to bestow, but instead of it gave silver and sometimes nothing, yet in all those cases did cure, and those that were cured by his blood wore no gold

"Now whereas upon the loss of the gold some have found damage, I would know, whether any of them were relieved by the wearing any other gold then what the king gave them"

## Critical Review

### ALLERGY AS RELATED TO OTOLARYNGOLOGY AND PEDIATRICS

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IN A PREVIOUS review in this Journal, Smyth' made a comprehen-I sive survey of the most important articles appearing in the literature on the subject of allergy in general In another review, Dean' gave an interesting account of the recent advances in pediatric otolaryngology In the present review, it is intended to make an analysis of those publications having a relationship to both the otolaryngologist and the nedistrist The commonest manifestations of allergy are those which occur in the nose and paranasal sinuses, and while this area may be the only site involved, allergy is frequently manifest in other parts of the body and in other ways. It is often necessary for the otolaryngologist to determine whether some condition such as headache, gastrointestinal disease, bionchitis, asthma, eczema or recurrent colds, as diagnosed by the pediatrist, is associated with a nasal allergy presence of a definite usual allergy should suggest the allergic origin

of the various conditions mentioned

The responsibility of diagnosis and treatment of certain infections of the upper respiratory tract in children, such as acute and chronic rhinitis, sinusitis, tracheitis, bronchitis and laryngitis, should rest on both the otolaryngologist and the pediatrist. Although these disturbances may be due to infection, they are frequently manifestations of allergy, and if proper treatment is to be instituted, the intections must be differentiated from those conditions of an allergic nature also be emphasized that an infectious process may occur in a child known to be allergic, so that attention should be directed to this fac The points relating particularly to tor as well as to the infection coexisting allergy and infections in adults have been emphasized in former communications \$, 4, 5, 6, 7 In the Pediatric Allergy Chine of the Washington University Dispensary, we have had opportunity to observe a large number of children with seasonal and nonseasonal nasal allergy with and without associated bronchial asthma Cases of eczema and selected cases of gastrointestinal disease, headache, frequent head colds, paranasal sinusitis, recurring acute bronchitis, chronic bronchitis, bronchiectasis and various forms of dyspinea, have been observed with the idea of determining whether or not allergy was a factor in the production of these conditions In many of these cases the diagnosis of an associated nasal allergy suggested the allergic origin of the other condition It was found that it is especially important in dealing with the respiratory conditions to determine whether we were dealing with a pure allergy, an infection or an allergy with superimposed infection. A proper diagnosis of these various conditions and their relation to allergy can be established only after taking a detailed clinical history and making certain physical and laboratory examinations

Reference to the relationship of allergy to infection may be found only in the most recent literature on the subject of frequent colds, sinusitis, and bronchitis. The relationship of sinusitis and acute nasal infections to asthma and other forms of allergy has been greatly clarified by a careful study of the differential diagnosis between al lergy and infection, and has been emphasized by Dean, 2° Carmack 10 Richards, 11 Brown, 12 Cassady 12 and McLaurin 14

Cohen and Rudolph<sup>11</sup> in a recent report emphasized the importance of differential diagnosis between allergic and infectious conditions of

the upper respiratory tract in children

Consideration must be given to the factors which indicate the al lergic basis for the complaints. These are (1) the family history, (2) past history of allergy (3) presenting symptoms, (4) skin tests and (5) blood examination for cosmophilia. From the otolaryngologic standpoint, the following factors are to be especially considered (1) the masal symptoms (2) rhinoscopic examination, (3) misal smears, (4) reentgenologic examination of the sinuses and (5) histologic examination of the masal and sinus tissues

A detailed clinical history in these cases is of the utmost importance A study of the family history of allergic patients will reveal the fact that a much larger number of relatives are found to be affected with manifestations of allergy than is the rule in other families studies of Cooke and Vander Veer 10 Spain and Cooke 17 Adkinson18 and Balyeat, 19 show positive family histories in 40 to 60 per cent of the asthma cases in their series Among the normals, investigated in some of these studies a positive family history occurred in only 7 to 9 per cent Coca ond his associates have pointed out that heredity not only plays a part in the choice of the individuals affected, but also more or less determines the nature of the malady by designating the The evidence seems to indicate that the predisposed shock organ age of onset is more or less predetermined by hereditary factors as is also the nature of the atopens or allergens to which the patient tends to become sensitive Cooke and Spain, 21 and Cooke 22 have reported that when there is a positive history of allergy in both parents, ap proximately 75 per cent of the offspring will develop manifestations of allergy before the tenth year. With a single inheritance 31 per cent, and with no history of inheritance 20 per cent develop manifestations before the tenth year Of all children with bilateral inheritance 70 per cent will eventually develop symptoms and of those with a uni lateral history about 50 per cent. The earliest manifestation of al lergy which appears in infancy is eezema. This is often replaced by the respiratory symptoms later During the first three years of life foods are the outstanding factors and after this age the inhalants Hypersensitivity to foods and infections in are to be considered infants, tends to disappear between the age of five and ten years but hypersensitivity to the inhalants tends to persist. According to Rowe,22 however, food sensitization may remain as a major factor or the sole cause of symptoms into adult life, in spite of the fact that skin tests may be negative Asthma developing between the age of three and thirty years is usually caused by the inhalants. The onset is often gradual and is usually preceded by the masal manifestations. Asthma appearing after the age of thirty years is usually associated with infec tions and is also gradual in its onset. The clinical history frequently shows that the allergic child has other manifestations of allergy such

as eczema, urticaria, gastrointestinal symptoms, asthma or hay fever, either recently or in the past. In some cases, the manifestations of the food allergies are not acute and lead to evidences of mild disturbances such as anorexia, malnutrition, nervous irritability and sleep lessness. The examination of the blood usually shows an eosinophilia and positive skin tests are usually found. In the infectious cases due to infection without allergy, the family history is usually negative for hypersensitive individuals, rarely are there any other manifestations of allergy, the blood shows no significant eosinophilia and skin tests are negative.

Since the clinical picture of acute rhinitis and acute paranasal sinusitis is well known, only a brief consideration of this phase of the subject is necessary. Attacks of acute rhinitis usually run a typical course, lasting from five to twelve days, after which there is usually an immunity lasting several weeks or if the attack is uncomplicated, there is a complete resolution of the process. There is generally a history of physical exposure or of contagion The attack is accompanied by fever, malaise and other well-known symptoms is not related to food or inhalant contacts. The examination of the nose shows a swollen, usually hyperemic membrane with mucopurulent secretion which shows the presence of numerous pus cells genograms of the sinuses are not often significant. When acute rhinitis does not undergo resolution within a reasonable period of time, however, a complicating sinusitis usually manifests itself with the symptoms of persistent mucopurulent discharge, positive roentgenographic findings and general symptoms of infection. In chronic paranasal sinus infections, it is particularly important to differentiate between allergy and infection and to take into consideration that an existing chronic infection may be associated with an allergic process

It is also important to mention that the manifestations of allergy may be noted for the first time following one of the common contagious diseases of childhood Peshkin<sup>24</sup> found that pertussis was the most frequent causative disease. Measles and scarlet fever were also mentioned. Other infections such as pneumonia and influenza may also be responsible. What appears to be a sinus infection following these diseases should, therefore, be carefully investigated because of the fact that nasal allergy may originate in this manner.

In the consideration of allergy as it manifests itself in the nose and paranasal smuses in children, information in the history regarding the criteria which characterize the state of hypersensitivity must be obtained, but in the analysis of the clinical history, physical and laboratory findings, one may expect great variations. Sometimes diagnosis is prompt and easy but often it can be established only after periods of observation We usually think of the nasal symptoms as being characterized by attacks of sneezing, nasal obstruction and the discharge of serous or mucous material Picking at and itching of the nose, rubbing of eyes and clearing the throat or a dry cough may be prominent and characteristic symptoms There are a great many instances, however, in which all of these symptoms are not present though sneezing may be a prominent symptom, in children it is frequently absent The child may show only signs of nasal obstruction and nasal discharge Obstruction may be more or less constant or it may be intermittent. Discharge may be profuse and watery or it may

be entirely postnasal in the form of thick mucus. A child may exhibit only the symptoms of transitory attacks of meal obstruction of nasal allers, are usually not related to contagion but frequently appear with an inhalant or food contact. Fever or constitutional symptoms are rarely present. Typical attacks are usually recurrent every few days or every few wicks. In certain cases however they may appear with long periods of remission resembling in this respect attacks of acute rhinitis. It is important to note other manifestations of allergy may exist in other parts of the body with those in the nose Children often have gastrointestinal symptoms such as gas belching distention, cramps pain or diarrhea at the same time Local or gen eralized headache, augioneurotic edema bronchitis or asthma may also Attacks of nasal allergy may alternate with attacks of acute rlunitis Following an attack of acute rhinitis or broughtts nasal symptoms may become more severe or they may entirely subside for several weeks. Acute infection frequently increases the degree of hy persensitivity in allergic individuals often precipitating symptoms after a period of apparent quiescence. The patient therefore may react to a slight exposure which in the absence of infection would not be sufficient to enuse symptoms. Agail symptoms may subside dur ing the existence of some other manifestation of allergy such as urti caria Nasal symptoms may be present or absent with allergic head During attacks of nasal allergy we must bear in mind that re actions are also occurring in the paramasal sinuses. The swelling of the liming membranes the increase flow and consequent retention of secretions may produce local pain or headache

On examination of the nose in allergy characteristic changes in the mucous membrane are found they are characterized by a pale swollen edematous appearance of the turbinates and an abundance of mucoid secretion. Gross polypoid changes are rarely present in voung chil dren but may be found not infrequently in older children. During the state of active symptoms, these changes are easy to recognize but during the quiescent periods, the membrane may appear quite normal or may appear pale and dry with thick mucoid secretion, and the picture may not be easy to recognize.

The most important laboratory method used in diagnosis is the microscopic examination of the musal secretions for the presence of In the collection of nasal secretion for examination it is necessary to obtain mucous material because it contains the cells which are to be examined Thin watery material usually shows very few if any cells In children instead of swabbing the secretion from the nose simply direct the child to blow the nose on some waxed paper and transfer the material to glass slides. It is advisable to make two or three smears because the cosmophiles may be found only in certain parts of the specimen They may be entirely missed upon the exami nation of only one slide. The smears should be stained by Wright's stain in the same manner as blood films The number of cosmonhiles observed may not be constant because several factors which cause them to appear may vary During the complete mactivity, they should be absent Frequently however during an apparent stage of mactiv ity, there are mild transitory reactions which do not give rise to noticeable symptoms vet the secretions will reveal the presence of many cosmophiles If an acute infection occurs they may be either present or absent. They may be found in considerable numbers along with the

pus cells or neutrophiles, or due to the relatively large number of pus cells, they may appear diminished. As the cold subsides, the pus cells disappear and the eosinophiles continue and reappear in relatively increased numbers. In some cases, however, there may be few or no eosinophiles during an acute rhinitis. In these cases, the manifestations of allergy may entirely disappear for a certain period of time following the subsidence of the acute infection. The gross examination of secretions without cytologic study has proved to be very unreliable in drawing conclusions as to the presence or absence of pus Clear secretion may show pus cells or eosinophiles or both. Yellowish mucopurulent secretion may contain pus cells, both types of cells, or may show only large numbers of eosinophiles.

If a chronic infection of the paranasal sinuses becomes associated with an allergic process, both eosinophiles and pus cells are found in the secretions. An exacerbation of the infection may result from repeated acute infection or from allergic reactions following contact with an offending allergen. Allergic reactions may cause considerable increase in an already existing edema

In the histologic examination of the nasal tissues in allergy, in infection, and in allergy with infection, the picture is comparable to the cytology of the nasal and sinus secretions. Edema of the tissues is an almost constant finding in allergy and is usually very marked, but it may also be present with infection. Eosinophilic infiltration of the tissue is a characteristic feature of allergy, while acute rhinitis is characterized by some edema and neutrophilic infiltration. In combined allergy and infection, both types of cells are found. Lymphocytic and plasma cell infiltration are present in both types of reactions. Chronic infection produces connective tissue proliferation in various degrees.

The roentgenographic findings in the paranasal sinuses in allergy as well as in infection, are positive in a very large percentage of cases and cannot be differentiated from each other. In allergy, positive findings may be purely transitory, being present at one time and absent at another. It is unfortunate that in many of the reports in the literature on paranasal sinus infection in children, so much reliance has been placed upon roentgenographic findings and the cytology of the secretions has been so greatly neglected.

Too much reliance should not be placed on the performance of skin tests and their interpretation in the diagnosis of allergy. A positive reaction indicates nothing more than a clue as to past, present or future possibilities. Its significance must be determined by further clinical observation. On the other hand, negative tests do not rule out the possibility of existing allergy. Kalin, for example, has found that skin tests in infants and young children, suffering with pollen asthma and hav fever, are frequently entirely negative or only slightly positive. He believes that such weak positive tests actually indicate a minor degree of hypersensitiveness and he urges that advantage can be taken of this low degree of sensitiveness in initial or early stages of asthma to render these children free or nearly free from attacks by proper precautions against pollen overdosage.

In the management of acute and chronic tracheobronchial conditions in children, the otolaryngologist is frequently called upon to determine the possible relationship to certain pathologic disturbances in

the nose and throat ( ooke has described a peculiar cough which he frequently found associated with allergic coryen. The cough is vio lent and paroxysmal in nature and is frequently accompanied by vomiting. He believes it is caused by hypersensitiveness and discusses the difficulty of differentiating this cough from pertusus Dukers has also called attention to the occurrence of allergic bronchitis and states that it is often incorrectly diagnosed as tuberculosis chronic bron chitis and bronchicotasis \ Brown2 asserts that a spasmodic bron chitis sometimes mangurates an attack of asthma in children believes that in children this type of bronchitis occurs more frequently than true bronchini asthma Rowe 23 Colmes 25 Colmes and Racke mann20 and Kahu20 state that a dry arritating cough is a symptom of sensitization of the trachea and the bronchi and point out the importance of recognizing these atypical cases of asthma. The examination of the nose in these cases may show the picture of allergy or infection Attacks of asthma may follow immediately an attack of pasal allergy An acute infection of the nose may also precipitate an attack of al lergic bronchitis or asthma Walzer states that when infection pre cipitates attacks they usually occur several days after the onset of the infection, while in cases of pure allergy the attacks usually are produced immediately The presence of upper respiratory infection therefore, such as the common cold paranasal sinusitis and tonsillitis 18 often responsible for the precipitation of an allergic bronchitis or asthma The proper treatment of these upper respiratory conditions increases the resistance of the patient and prevents the occurrence of the infections and thereby simplifies the management of the allergy

In the treatment of these cases it is evident that the control of the allergy is of primary importance. An attempt should be made not only to eliminate the offending allergenic substances but to eliminate if possible all nonspecific factors. The nutritional state of the patient should receive due consideration. All infection such as that existing in the paranasal sinuses teeth tonsils and adenoids should be eliminated in cases in which these procedures are indicated. In the performance of surgical procedures it is particularly important to avoid the stages of active allergic symptoms, thus is especially true regarding active hay fever. All cases of allergy should be under control before resorting to surgery. In children, as well as in adults the observations of Rackemann and Tobey, 31 Bullen 22 and others have shown that in a large series of cases the removal of the tonsils and adenoids has shown no definite influence in the improvement of the existing asthms.

Walzers states that the removal of the tonsils and adenoids in an allergic individual is frequently followed by the development of nasal allergy or asthma or both. Many cases of pollen hay fever or asthma date the onset of their first symptoms from a tonsilicationy and it is impossible to consider the coincidence of the two conditions or events as purely accidental. The question may well be raised as to whether the infection which instigates the procedure may not have been responsible rather than the operation itself. We have found that in many cases of children with allergy a tonsilicationy was definitely in dicated, but with careful attention to the control of the allergy, the occurrence of untoward complications could be avoided with reason able safety.

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## American Academy of Pediatrics

### Proceedings

# THIRD ANNUAL MEETING OF THE AMERICAN ACADLMY OF PEDIATRICS

MONDAY APTERNOON SESSION June 12, 1933

### Round Table Conference on Allergic Conditions

Leader Dr Bela Schick, Assistant Dr J E Gonce

DR SCHICK.—It is my intention to make only short introductory remarks—1 would like to have a very lively discussion which need not be limited to the problems I shall mention

When one talks about allergy, it should be remembered there are two things to be considered: First, allergy as a very wide term meaning all kinds of altered reactivity of the organism due to previous administrations of a foreign substance Every disease both the neute ones and to a greater extent all chronic diseases, may show allergic features. Second, we can include in our discussion the so-called allergic diseases such as asthma, hay fover, excema, urticaria, etc. A better title for these diseases would be 'hyperergic diseases.'

(Dr Schick abstracted his remarks as printed in the February 1933 issue of the JOURNA of PEDIATRICS.)

DR. J E. GONCE (Madison Wisconsin) —In opening the discussion of Dr Schlick's summary on the general subject of allergy, I would like to emphasize the fact that the proper handling of cases of asthma hay fever occome, etc., is an intricate procedum one which requires the closest attention to every detail and familiarity with the latest theories and practices of the specialists in this field of medicine A casual interest in allergic disorders is certainly paralleled with had

A few of the practical points connected with the diagnosis and trestment of al lergic disorders which impress me as being of fundamental importance are concerned with (1) the selection of materials (2) the use of guides in pollen therapy and (5) methods of administration of protein extracts.

(1) The materials used for sensitisation tests and for desensitisation must be absolutely reliable. In my experience glycero-saline extracts are more sensitive but on account of the danger of causing constitutional reactions must be preceded by scratch tests thereby making their use too expensive for general use. Many specialists in allergic disorders use powders for scratch testing but most of these men manufacture their own in order to be certain of their allergic netivity. Where it is impracticable or impossible to prepare protein extracts for one s own use as is the case for most of us it is necessary to exercise the greatest care in the selection of a commercial manufacturer from whom to purchase extracts. In this connection an experience of mine last winter is callight ning. In answer to questions concern

ing the detailed preparation of pollen extracts, one well known firm replied, "In the beginning the writer would say that our house is probably not in any way different from any other commercial house and while we have no objection to offering the general routine of our methods of manufacture, nevertheless, there are many items connected with the manufacturing of proteins and pollens that are considered manufacturer's secrets" Another house hedged on some of the questions and the third firm addressed completely answered all questions and denoted their willingness and even desire to supply all information within their power to furnish. Now that Stull and Cooke and their coworkers seem to have definitely shown that the allergically active factor of pollens resides in the albumin fraction and have suggested the standardization of pollen extracts on a protein nitrogen basis, it is quite likely their recommendations will be accepted and the preparation of various extracts for testing and therapeutic purposes become a uniform and reliable procedure practiced by all commercial houses alike

In regard to the stability of extracts prepared for therapeutic purposes, I believe everyone at the present time agrees that the glycero saline extracts are the most stable. In a recent issue of the Journal of Allergy, it is stated that 31 out of 73 specialists use extracting fluids containing glycerine.

(2) The use of various guides in pollen therapy is now a well established procedure and may be considered under three divisions. First, determination of the patient's skin sensitivity to serial dilutions of the offending pollen will prevent waste of time by an unnecessary number of weak doses and will also help to avoid the administration of initial doses large enough to cause constitutional reactions

Second, application of skin tests in serial dilutions during the course of treat ment is of decided value in estimating the frequency and number of doses neces sary to bring about satisfactory desensitization in the individual case. Although it is not universally agreed that pollen therapy influences the severity of the response of skin tests, the opinion of many men, especially Dr. Duke of Kansas Citrand Dr. S. T. Brown of Washington, who use large doses, is that there is not only a relationship between pollen therapy and skin sensitivity but a diminution in skin tests may be indicative of a lessened chinical sensitivity as well. In proof of this belief, it has been shown that failure to obtain clinical improvement in a hay fever patient whose skin test has been changed by therapy from a strongly positive to a weakly positive or negative reaction, may be due to extra pollen sensitivity

Third, the extent of the local reaction from each subcutaneous injection of pollen extract is of considerable help in estimating the dose of the following in jections. In using this guide, it is necessary to place the injection superficially in the subcutaneous tissues because the deeper method of injection is less apt to produce a local reaction.

(3) As to the method of administration of protein extracts, I would like to en courage the use of the Duke method. Although there are certain specialists in al lergic disorders who like to poke fun at the use of the tourniquet and adrenalin ephedrin mixture, I feel quite certain this method makes the administration of protein extracts almost "fool proof". It has several advantages in that it permits rapid increase in the amount of protein extracts given, the administration of doses of a size far beyond those of the unmodified injection method, and, in the case of perennial treatment, permits the lengthening of the interval between injections to two, three or four weeks without danger of constitutional reaction. Dr Duke himself says this interval may be stretched to two or three months

I personally have dropped the use of the tourniquet because soon after adopting the Duke method of injection I noticed on the third, fourth or subsequent application of the tourniquet, the child's arm immediately became terribly discolored. Con sequently, I leave off the tourniquet and minimize the possibility of injecting directly

into a blood vessel by first drawing back the plunger of the syringe before making the injection. The mixture of one-third adrenalia and two thirds ephedrin (8 per cent solution) in amounts of 0.2 c.c. combined with the extract causes an almost immediate blanching of the skin where the injection is superficially placed and the rate of absorption, I am sure is retarded just about as much as when the tourniquet is used

I have only a couple more things to say I happened to think when Dr Schick was speaking of status asthmaticus, that our adult medical service has had oc easion to treat several patients with this condition by means of bronchoscopic cleansing of the trachen and bronchi One patient is a traffic officer in Madison who obtains immediate relief by this treatment. He then remains free from symptoms for many months.

In closing I would like to ask Dr Schick to state his opinion of the relative merits of the ideas on tuberculosis of Heimbeck of Oslo and Myers and Stewart of Minneapolis

DR SOHICK—About the influence of repeated injections on the intensity of the skin reaction, it can be stated that a large dose may have an attenuating effect upon a following skin test. Similar observations are made in tuberculin treatment. Frequently a Pirquet test made twenty four hours after a large dose of tuberculin (1 mg) will be smaller or even negative. The Pirquet test will become positive again after an interval.

Asthmatic patients free from attacks for several years still may have about the same intensity of the skin reaction as at the time of attacks. Apparently the reactivity of the skin is dissociated so to speak from the asthmatic reaction of the respiratory tract. This may be due to treatment or to aging (maturing) An eccematous patient may lose his execua and exchange the eccema for an asthma. Apparently the skin changes its reactivity and the respiratory tract starts to react in an abnormal way. In eccema and asthma we frequently find that when the eccema improves the asthma gets werse or as the asthma gets better, the eccema appears. There is an interrelation between the two organs the skin and respiratory tract. There can exist a complete dissociation so the execua can disappear while the asthma remains. It is possible to obtain a very strong skin reaction to a certain protein although the asthma is not due to this protein or you can encounter just the reverse a relatively weak reaction (± reaction) to a protein which is responsible for the asthmatic attack.

As to the use of adrenalia and the tourniquet, these procedures are helpful—both slow down the absorption. Adrenalia brings about a vasoconstriction—the tourniquet compresses the lymph channels—In all cases where we suspect the patient is very sensitive to the substance to be injected—i.e. horse serum such procedures should be taken into consideration especially the use of the tourniquet. The same can be accomplished in an easier way by injecting higher dilutions of the substance.

The story of a policeman who was treated during his attacks by sucking out the plugs with the bronchoscope is very interesting. Of course bronchoscopy is a little more dangerous in children than in adults.

Concerning the idea of Heimback in Oslo as to whether it is better to be infected with tuberculosis and become reexposed or to be infected with tuberculosis with no previous tuberculous infection I read very carefully the article by Dr Stewart in which he expresses the latter theory — The prevailing theory is that the first infection with tuberculosis in a mild form immunizes to a certain extent against a reinfection later in life. The immunity of the adult against tuberculosis is based upon the effect of the preceding infection in childhood. In an institution for the treatment of tuberculosis in Oslo Heimback divided the nurses into two groups in the one were the tuberculin positive and the other, the tuberculin negative nurses.

He studied these two groups of nurses during their stay, as they were exposed to tuberculosis and found the nurses who had a positive tuberculin test on admission were better off in that not such a large number of them developed an active tuber culosis. Many more of the nurses who came in with a negative reaction indicating they had no previous infection with tuberculosis, developed active tuberculosis. He used this observation as a reason to introduce active immunization with B C G against tuberculosis among nurses and he was very much satisfied with it

Dr Stewart found in his examination of 10,000 school children that several children who did not show any form of tuberculosis for several years before, on exposure developed a very mild tuberculous infection. On the other hand, children who were positive before to tuberculin and had some calcified foci in their lungs, developed a very active tuberculosis.

I still believe that much depends on the quantity of tubercle bacilli entering during exposure. If an individual has been exposed to a very large amount of in fection, this person is in danger whether he had a previous infection with tuberculosis or not. We are afraid of massive reinfections, as the immunity against tuberculosis conferred by a previous infection is only a limited one. It is sufficiently strong for a mild reinfection but it does not help against a very violent one. I think it is too early to accept Stewart's viewpoint as final. We may still adhere to the idea that a small first infection produces a certain amount of immunity against a new in vasion.

(Discussion by Dr Bell not sent in for publication)

DR BLATT (CHICAGO) —Dr Schick, you expressed a thought I believe should be stressed a little more, namely, the relationship between allergic phenomena and infectious diseases. In 1911 when I worked in your dispensary in Vienna, you emphasized the fact that some of the kidney complications of scarlet fever were allergic. At that time, you expressed the thought that in all probability the glomerular nephritis coming on in the third week of scarlet fever was a secondary phenomenon not due to a local streptococcic infection but probably to an allergic phenomenon of streptococcic origin. I have always felt that expression was worth passing on and nothing in the interim has changed my belief in this statement.

I think the term "allergy" is not satisfactory, as it is applied now. It has seemed to me that all forms of dermatitis should not be classified as allergic even though they express somewhat similar phenomena. For instance, a dermatitis due to sun rays, a dermatitis due to an irritant, a dermatitis due to feathers, a dermatitis due to some other immediate contact agent, should not be classified with those al lergic phenomena associated with changes in protein sequential to hier dysfunction or direct gastrointestinal absorption without liver detoxication. It is quite apparent that the same principles which underlie Bestedka's attempt at immunization through systemic means is influencing us in our allergic immunization. As you stated, it is quite possible to apparently arrest the asthma and have the skin retain its tendency toward urticarial phenomena on an allergic basis. I think many of these so called allergic phenomena are much more closely related to dermatitis and are in flammatory rather than primarily exuditive

Based upon findings of the United States Department of Agriculture, the milk shed of Chicago is definitely known and the open pasture has definite dates. In the spring when the cattle first are turned out to pasture, large numbers of weeds are ingested and many of these contain active glucosides which may be the source of some of our allergic skin phenomena such as lichen urticatus

As to infection with tuberculosis, Dr Jasse has expressed himself as being in accord with Stewart's opinion and I am accepting this theory. The large amount of pathologic material at Cook County Children's Hospital seems to show many serious effects of superimposition of tuberculous infection rather than primary

sensitization and primary complex dissemination. Last winter I saw a number of postmortem examinations on generalized tuberculosis with a primary complexion that was apparently entirely healed and I am of the opinion the primary vaccination with tuberculosis was not effective in protecting these cases. From time to time I have seen a general dissemination from a primary complex but these cases are comparatively rare.

I would like to ask a question in regard to the use of dextrose which reports from Guy a Hospital scen to favor. It is thought its effectiveness has to do with liver protection possibly that it has to do with increasing of the detexified reaction in the liver rather than any relationship to the blood sugar content primarily. I tried this procedure in two or three cases, in one of which I had very unusual success. Not only did the patient on adolescent girl who had asthma all her life react favorably so far as the asthma, was concerned, but she gained a large amount of weight.

DR. SCHICK.—The first question was about allergy in infectious diseases especially in searlet force. Dr. Blatt quoted me correctly. I believe that fourteen days or three weeks after the enset of searlet fever a period of increased sensitiveness starts and all postecarlatinal diseases are the expression of this allergy (inmediate) to a germ having survived from the time of the original scarlet fover process. Some authors feel that the first part of the searlet fever process is also allergie in nature. I think my original idea is more correct that the first symptoms in scarlet fever are due primarily to a toxic substance and only the postecarlatinal diseases are allergic in nature. It is interesting that similar observations have been made in typhoid fever and measles. In order to be careful as to how far one should go with theories, I have left open the answer to the question whether the nephritis and the other postscarlatinal conditions are the effect of the streptoceccus and its toxin.

Dr Blatt pointed out that it is very hard to apply the term allergy to so many different types of symptoms and I agree. However allergy is a necessary term; we need such a word for the 'altered reactivity' If we make clear that what is especially important from the practical viewpoint is the hyperergic or anaphylactic reaction there will not be much room for minunderstanding. Severe anaphylaxis, characterized by a shock endangering life does not occur so frequently If one considers how many millions of injections of serum are given and how few cases of real anaphylactic shock are observed one will realise that it is fortunately very rare. Anyone who has seen such an anaphylactic shock will never forget it and will be very cautious thereafter in injecting serum, particularly intra venously

The good effect of the injection of glucose is difficult to explain. It may be helpful in stimulating the function of the heart. Another factor may be the improvement of the liver function as during the anaphylactic shock, the glycogen of the liver disappears. The circulation also will be benefited by the supply of fluid

DR. LEWIS WEBB HILL (Boston) —There is a large group of skin conditions in infancy we call infantile eczema and I am quite sure we are in reality dealing with a number of different, probably unrelated diseases. We must split apart this group as far as we can, by close observation of the skin and very careful study as to etiology for we never will get anywhere with infantile eczema until we do

If one considers the history of dermatology in the last fifty or seventy five years one sees that is what is happening. The dermatologist of olden times was confronted by an individual with a red skin eruption and he gradually noticed these skin eruptions were different. Scables used to be called examn, so did psoriasis and pityrinais rosea. We must go through the same process with our infantile

eczemas before we can really understand them. I believe 60 to 70 per cent of the cases of infantile eczema are of allergic origin but there are, as Dr Bell has said, a good many causative factors other than allergy. I think we must take fungus infestation into consideration. In adult dermatology at the present time, there is a tremendous interest in fungus infestation of the skin with the epidermo phyton group and the Monilia albicans or thrush group

I am very much interested in this as regards infinits and children and am trying to determine by intracutaneous skin tests with various fungi, what cases can be put into the fungus group. The difficulty is that oftentimes food allergy and fungus infestation occur together and I am quite sure it is the allergic child who is especially susceptible to fungus infestation. This work is not far enough along at present to say definitely that we can, by means of skin tests or by any other method, determine exactly which cases are due to fungus infestation and which are not, because culturing the fungi from the skin means very little. Making scrapings of the skin and finding them under the microscope means little as they also occur on so many normal skins. Both of these methods are somewhat complicated for average use

Skin tests with various fungi show a fair number of positive reactions and I have brought a few pictures of what would seem to be fairly typical fungus eruptions. These pictures all represent probable moniha infection, that is, thrush of the skin. I have had positive tests in cases one would certainly call ordinary "eczema". Fungus infestation, however, is probably of relatively small importance in infantile eczema and we must go back to allergy to account for most of the cases.

We should do skin tests on most cases of infantile eczema as we get a good deal of information. This is perhaps more theoretical than practical because a great many times we find by the skin tests nothing whatever to help us in the actual treatment of the child. A five month old baby who has never eaten an egg may give a strong test to egg white. That does not help much in the practical treatment of that baby, but it does tell us that the baby is allergic and I consider the reaction to egg white in young infants a stamp of allergy. It identifies that baby as being of an allergic constitution and as Dr. Schick said, sensitization through the placenta is probably very common and I am quite convinced a great many cases of infantile eczema start by sensitization to egg white through the placenta.

Egg white is the most difficult of digestion of any protein and if one cats a raw egg, some of the egg white goes unchanged through the intestinal mucosa into the general circulation. Some time ago I got some serum from an egg sensitive child with eczema and injected a little into my forearm. The next day I ate some cookies and within fifteen to twenty minutes, a big wheal developed on my arm

I made some passive transfer tests for a baby with very bad eczema, whose skin was so bad I could not do ordinary skin tests. I put into the arm of the baby's father about 30 injections of the baby's serum in very small amounts and unknown to me, this man was in the hibit of cating a raw egg every morning for breakfast. He are a raw egg the next morning and his arm was enormously swellen for two or three days and the reaction persisted for several weeks. The serum of an eczematous child sensitive to egg may be a powerful thing and if passive transfer tests are done, we must be careful to use only very small amounts of serum or to dilute the serum considerably before injection.

I use a type of skin scratcher that I devised. It is not so easy to do skin tests with a needle or a knife on a baby, as the baby struggles, he has to be held down with one hand, and it is very difficult to make the scratches exactly the same depth and length and it is important to do so in order to read the tests accurately. This instrument is simply a small punch, like a leather punch, it is sharp on the end and makes a circular scratch

I have derived a great deal of pleasure and profit from reading Dr Moro's book on Eczema It is a masterly exposition of the subject but, as Dr Schick said, it is very interesting to see how little attention the Germans have paid to allergy and skin testing Dr Moro in the preface of his book says he did not attack much im portance to skin testing until he had written about half the book, he then decided to try them and see whether they were worth while and he became most enthusiastic about the allergic theory of exemus.

He believes sensitization to egg in utero is the primary step in the development of a great many infantile excemss. The child being stamped as an allergic in dividual, the allergy may branch out in a number of different directions and he may become sensitized to a great many other things as well and have a multiple sensitization. Why some infants become sensitized and some do not is obscure; it may depend upon hereditary factors, or possibly on quantitative differences in the allergen ingested. This is a very attractive theory and fits in well with the facts of excema as we observe them.

Another interesting thing about egg white, Woringer who writes so well on allergy believes there are two kinds of egg sensitive babies, one in whom there is simply skin sensitivity and no antibodies in the blood the other in whom there is skin sensitivity plus antibodies in the blood. He believes an excematous child can not be cured by removing egg from the diet even if he is sensitived to egg and I am rather inclined to agree. I have seen innumerable older children sensitive to egg with positive skin tests, but I have never seen one cured by removing egg from the diet. He also believes extma cannot be made worse by feeding egg. He looks upon infantile excema as being not exactly an allergic phenomenon but a para allergic phenomenon going along with allergy, the whole substrutum of the process being sensitivity to egg white or egg yolk with of course in some cases, primary sensitivity to milk, wheat or any other allergen as the case may be.

Dermatology at present is dominated very much by Bruno Bloch of Zurich and his ideas of exema. Under his influence the German school confines itself to calling exema an external dermatitis. A poison ivy or any other external dermatitis is exema and nothing else is. A good deal of confusion has arisen on that account because in this country the dermatologists have a much broader definition of exema. The followers of Bloch look upon adult exema as a contact dermatitis and they determine sensitivity by means of the patch test.

I believe in certain infants we do get sensitivity to external things. I have had patients sensitive to wool silk eat fur dog hair or what not, but I believe the vast majority of reactions come from the ingestion. There are no metabolic changes particularly characteristic of infantile exemn. All metabolic researches have de veloped nothing of any great moment

With regard to the use of milk free diets, Stewart and I some years ago developed Sobee, made of soy bean flour and oilve oil etc. because it seemed we never would be able to tell exactly what rôle milk played in the development of infantile exemu until we could have a satisfactory diet without milk for the baby. I have fed a great many infants on this food and I believe one must not expect too much of it it is not a curveall for exemu by any means. If the exema is due to milk sensitivity it will undoubtedly be cured by Sobee feeding provided there are not a great many other sensitivities. If the baby is sensitive to egg and milk and a number of other things, he is not very likely to do well with Sobee feeding. If the exema is purely and primarily a milk case the results are very satisfactory. When we first prepared Sobee, we made it of barley flour and later with purified cornstarch on account of the objection Dr. Bell has spoken of All the Sobee for some time has been made with purified cornstarch and I believe before long arrow toot starch will be used instead following the suggestion of someone in California.

Certain changes in the protein undoubtedly take place when milk is heated very hot. It is probably true that the lactalbumin is rendered less allergie by prolonged heating. The case in is changed very little. I am skeptical about "denntured" milks. I believe that in some cases of mild milk sensitivity, if the idiosyncrasy is due to lactalbumin alone, the heated milk may do very well but, on the other hand, if the idiosyncrasy is due to both case in and lactalbumin, as it frequently is, or to case in alone, heated milk will not do much and I believe a milk free diet is very much to be preferred.

I have been able to get very definitely positive skin tests with powdered milk heated to 130° C for one hour, just as large skin tests as I would with pure casein I think the subject of heated milk deserves a closer and much more careful study than has been given it as we really know very little about what changes take place in casein when it is heated or indeed if any important changes do take place

I have had very little experience with either specific or nonspecific desensitization because after studying the literature and talking with a good many people, I concluded it was probably not a very satisfactory procedure for private practice particularly. It takes a good many injections, there may be fairly severe reactions, results are pretty uncertain and if we do get an immunity, it lasts only a comparatively short time. I firmly believe we have no answer to infantile eczema until we have some method of rendering an allergic child nonallergic and that method will come some time in the future through some means of nonspecific therapy. If we have a child with eczema or asthma who has a multiple sensitivity as almost all of them have, it is absurd to expect to cure him by taking away all the things to which he is sensitive or to desensitize him specifically. Much of our treatment of infantile eczema is very crude and some of it rather silly, but I believe we will progress as time goes along

DR. CHARLES SCHOTT (Cincion) —Dr Schick, have you had any experience with the formic acid injections in eczema?

DR SCHICK—We have no experience in eczema though we tried them in asthma. We had some cases which responded to it but we dropped it after a while because the results were not so encouraging

DR S J LEVIN (Detroit) —I would like to ask about calcium therapy I know a great many variable reports have appeared about the value of calcium in eczema and asthma. I have found that calcium given intravenously is of con siderable benefit and is something we should give more attention to In status asthmaticus, we hesitate to use adrenalin continuously because of the short duration of benefit but calcium gluconate or gluco calcium given intravenously in amounts up to 10 c.c. has been found to be very effective in controlling these cases, it has helped a great deal in infantile eczema. Whether there is some fundamental calcium imbalance in allergy I do not know. Perhaps there is some disproportion between the calcium and the phosphorus and by elevating the calcium por tion, the normal relation between the calcium and phosphorus is obtained. I men tion this as a useful practical point in therapy and handling these difficult cases which come in during the pollen serson, or cases of status asthmaticus in which the ordinary methods do not seem to help

Another point I wish to make is the relationship of the skin tests to severity of symptoms especially in cases of pollen asthma. We have found it does not seem to matter much whether positive skin tests are present in large degree, whether they are present only in small degree, or absent entirely. The amount of pollen extract to be given therapeutically is not related in the majority of the cases to the height of the skin reaction. A child with pollen asthma who gives no positive skin tests whatever but whose symptoms occur at the typical pollenating season for

ragmeed may be extremely sometive subcutaneously to the extract of pollen and very minute doses may have to be used. Just the reverse may be true of the patient with extremely large skin reactions.

In any of these police cases, the police count in the air must be considered. Some men use high amounts of pollen extract and others use very small amounts. One cannot state that a certain amount of pollen is sufficient to cure any case of pollen asthma or hay fever We have a very high pollen count in Detroit Kansas City has the highest pollen count in America and Buffalo and Chicago are next, the fourth position is occupied by Detroit The same patient with the same sensitivity in an area with a low pollen count does not require many injections, but in the Detroit area we find we need tremendous doses of pollen extract almost to the point of obliterating the skin tests before we can obtain good relief. We give as a final dose from 1 to 2 c.c. of a 3 per cent solution which is a very strong solution for the average pollen case. On the other hand we see cases where we can obtain a dozage of only 0.05 c.c of a 1 in 10 000 solution and still get relief. It is such an individual question and the therapy must be so very detailed and adjusted individually for each patient that I believe one should not make a general rule. Especially one should not depend too much on height of skin reactions in relation to the size of dozes.

I also wanted to talk about the perennial treatment of pollen cases. Dr Schick is rather opposed to the continuation of perennial therapy and perhaps it does have its disadvantages but, on the other hand, it offers to the patient a possibility of erentually stopping pollen injections. Vaughan of Virginia gives figures indicating 50 per cent cures after three years of continuous therapy. In my own experience perennial therapy produces what may be called a permanent cure in eighteen months. It is a development in the treatment of allergy which must not be discarded too readily.

The extract of pollen or of foods should not be looked upon as a toxic substance. Whether the reaction of the body against this substance is autitoxic as in the case of diphtheris toxin still has to be shown

I have seen children subjected to series of climination diets that produced a very bad constitutional effect with general damage to the child in loss of weight and resistance to disease in the hope that by chance, some food would be climinated that might be causing the trouble. I believe we should not subject a child to such a serious method of diagnosis in the hope that by clance we will find the cause of their symptoms. It is far more accurate to do the skin tests first and avoid the pes sibility of injuring the child a general condition by a series of weird diets

DR SCHICK—The following theory about the effect of calcium can be evolved hen remember from the basic experiment of Chiari and Januschke croton oil put in the conjunctiva of a rabbit s eye produces a tremendous inflammatory reaction. This reaction was suppressed by giving calcium previous to the instillation of croton oil. The linings between the endothelial cells are tightened and made less per meable for exudation. I tried the calcium treatment in many cases and the result was not striking. You can find very much in the literature of twenty years ago about calcium therapy as a preventive measure against hay fever. There is some possibility of influencing the intensity of secretion and of inflammatory reaction on the skin and mucous membrane, but we should not expect a real cure of the condition.

I agree with Dr Hill that we should not put all the cesemas in one pot.

An hyperergic person is good soil for infections. Secondary infections complicating eczema must be considered. The eczema question is still not entirely solved, and we should be very cautious in our statements. DR LEWIS WEBB HILL—I wish you would say some more about nonspecific therapy in eczema. I know very little about it but feel quite strongly that is what we must have some time if we really want to deal with the disease satisfactorily. This is beside the question of local treatment, of regulating the diet, and taking away something we think the child is sensitive to

DR SCHICK—If we find some causative agents then, of course, these should be taken away, but, I am sure there must be other ways of treatment. If a child gets pneumonia or some other febrile disease, it is astonishing how quickly the eczema disappears and how different the skin looks within seventy two hours. We do not know what goes on in the system, but we do know that in some way nature is able to make the eczematous reaction disappear.

I have not had much personal experience with the nonspecific treatment and vac cine treatment in eczema. I hesitate to apply this treatment because I feel we are going a little too far in injecting all these different substances

(Remarks by Dr Franklin J Corper, Chicago, not sent in )

DR SCHICK.—I wish to express my personal opinion about the perennial treat ment. It is possible that interrupted treatment eventually brings about a hyper sensitization and perennial treatment prevents it. After interrupted treatment with tuberculin it happens that if one starts over again, one will find the patient more sensitive. I repeat that skin reactivity and asthmatic conditions do not always go parallel. Dr Peshkin showed me patients with pollen asthma who were absolutely negative to skin tests and still had typical pollen asthma. He could only obtain a positive test by testing the conjunctiva with dry pollen powder. There one sees the dissociation between the reaction of the skin and the reaction of the respiratory tract. The skin is very sensitive and the respiratory tract not so much so. There are also differences which may be explained partly by the different rate of absorption. If a substance is injected subcutaneously, the absorption will be slow, when given into a vein, the absorption is so rapid that a very large amount of this offending substance enters the system at one time.

(Remarks by Dr I. H Tumpeer not sent in for publication )

DR. SCHICK.—It has been my experience that tetanus antitoxin is more toxic than many other therapeutic sera. I have seen the worst kind of serum sickness after injections of tetanus antitoxin. As the purification of tetanus antitoxin is as thorough as that of diphtheria antitoxin, I am unable to explain the difference on that basis. I saw a child whom I had to keep under morphine for three days because of terrific joint pains. There was nothing visible on the joints. Other col leagues reported similar observations to me

We must differentiate between scrum sickness starting after a normal incubation period and one starting after an abnormally short time. If a child develops an intensive serum sickness eight to twelve days after injection, this has nothing to do with a previous sensitizing injection. The whole discussion should deal with the accelerated and immediate reaction.

An important question is whether or not there is danger of an anaphylactic shock in children immunized against diphtheria by toxin antitoxin in case the child must be treated later with a therapeutic serum. Such an occurrence is possible but extremely rare.

Another question I wish to discuss is the reaction observed in older tuberculous children and adults when toxoid (Anatoxin) is used for immunization against diph therm. The most satisfactory explanation is that tuberculous and other infections

change the general level of sensitivity to foreign protein so that the reaction is different from diphtheria toxin. Infants and children of preschool age show such reactions much less frequently

We should not go so far as to name everything allergie this would lead to con fusion I am wondering whether we have the right to explain sudden death in exceeding or hyperpyrexia on the basis of hyperergy. The mechanism may be a quite different one and we should look for other explanations.

No child of three or four years will be absolutely free from allergic features. Such features are usually mild, so that they have no special importance. There are different grades of reactivity in different individuals from mild to hyperergle reactions. Hyperergic reactivity has great clinical importance

DR. MOORE.—I would like to inquire whether there has been a study of defects in the endocrine system of the allergic childron. Barber has recently discussed the feeding of glands of internal secretion to certain types of children, the colicky child, the vemitter and I believe to the eczematous child. Has there been any work done on defects of the ndrenal as a causative factor?

DR. L. W HILL.--Would it be possible to settle the question of the danger of anaphylactic shock by looking for precipitins to horse serum in the blood?

DR. SCHICK.—I do not think so We had the greatest difficulty in finding precipitins in the blood. The human being is a very poor producer of precipitin.

### Academy News

The following have been appointed for the Nominating Committee Chairman.—Dr Samuel McC. Hamill Philadelphia Pennsylvania Dr E B Slaw, San Francisco Callfornia Dr Hugh Lealle Moore Dallas, Texas

Dr Sterling H. Ashmun, of Dayton Ohio has been appointed a member of the Ohio State Committee.

# News and Notes

### International Pediatric Congress\*

The third International Pediatric Congress, held in London on July 20 22, under the presidency of Dr G F Still, was attended by nearly 400 delegates from thirty countries. The inaugural ceremony took place in the Great Hall of the British Medical Association House, when T.R.H. the Duke and Duchess of York intended to open the congress and to welcome the members. H.R.H. the Duke of York, in expressing his pleasure at greeting so large a gathering, especially in view of the fact that this was the first international meeting in this country of physicians dealing with the diseases of childhood, made a few well chosen remarks, stressing the importance of pediatrics particularly on the preventive side. "Speaking as a father," he voiced the gratitude of parents far and wide who would benefit from the deliberations of the congress. The President and Sir Thomas Barlow expressed the thanks of the members to the Duke and Duchess for their interest in the congress and after the departure of the Royal visitors, the scientific proceedings began

The first main discussion took place on the subject of the nature of allergy and Dr Arnold Rich (Baltimore) spoke from the its rôle in diseases of children pathologic side and brought forward the results of experiments which demonstrated that in bacterial allergy the individual tissue cells are hypersensitive to the bac terial antigen and the allergic reaction is not dependent upon circulating intibody Ho stressed that all recent work went to show that allergy is not essential for im Experiments show that immunity can be separated from allergy and that neither of the two primary characteristics of immunity—the prevention of spread of bacteria and their efficient destruction—is dependent upon allergic inflammation for successful operation. He further pointed out that allergy be established with out immunity and acting alone, it lowers resistance to infection Hamburger (Vienna) dealt more with the chincal aspects of allergy, basing his remarks mainly upon the study of problems of tuberculosis by means of the tuberculin reactions Allergy could be shown to develop prior to the onset of the It was continuous but subject to the fluctuations caused by other diseases -by light, food and other so far unknown factors, and such fluctuations might be the cause of exacerbations. In his opinion, the tuberculin reaction was of great value in prognosis and tuberculin should be used to a greater extent for prophy Dr Pehu (Lyons), in a paper prepared jointly with Dr P Woringer (Strasbourg), described the clinical aspects of the allergic states of nonbacterial origin, enumerating the various substances capable of sensitizing the human or graism under the main headings of inhalation, food, drug and contact allergens He proceeded to give a description of the clinical manifestations of the nonhacterial allergic states in the various systems affected, pointing out how the different al lergens tended to affect different systems at various periods of life there were three possible causes of nonbacterial allergy sensitization after birth, sensitization in utero, and hereditary transmission by the germ cells, the last being of a specific nature or merely the inheritance of a predisposition Dr W R F Collis (Dublin) advanced the view that the same disease syndrome could be pro

<sup>\*</sup>British Ned J July 29 1933

duced by more than one organism provided that the body was in the state of al lergy, and he instanced crythema nodosum in this connection Dr H Ernberg (Stockholm) also discussed allergy in relation to crythema nodosum. Professor P Groer (Lwow) stressed the kinetic aspects of allergy, dependent upon two main factors—the susceptibility of the body and the power to react on the part of the body. He explained how these factors could be assessed accurately in the case of a disease such as tuberculosis. Professor G de Toni (Bologna), Professor R. Debré (Paris) and Dr B Ratter (New York) also took part in the discussion.

The discussion of the second day on the prophylaxis of milk borne diseases was opened by Professor A Pettersson (Stockholm) who dealt especially with the prob lem of tuberculosis. Not only was there the universal danger of bovine tuberculosis but in the speaker's opinion human tubercle were frequently introduced into the human body with milk He also mentioned the risk of infection with the organisms of undulant fever in those districts where infectious abortion occurred, but children under ten years of age fortunately appear to be either insusceptible or very slightly susceptible Professor G Bessau (Berlin) spoke of the saprophytic organisms in milk and their significance. The introduction of varieties of the colon bacillus by milk into the alimentary canal in children produced a completely different type of intestinal flora from that in the breast fed baby, for example, and many of the digestive disturbances in the artificially fed baby could be attributed to the spread of Bacillus coli to the upper parts of the alimentary tract. In contrast to the adult, where the presence of the coll bacilli in the bowel had no deleterious effects young bables might develop inflammation of the whole of the intestine, small and large, from this cause Professor G B. Allaria (Turin) explained that in Italy at present there was a strong movement for the improvement of the dairy industry and in the meanwhile it was of importance to seek an answer to the question of whether the advantages of giving raw milk as a "live" liquid and attempting to prevent bacterial contamination were greater than those obtained by giving a sterile milk at the expense of its vital properties. The speaker thought that the importance of the vital properties had been exaggerated and that in the present state of the dairy industry in the majority of countries, the only course was to purify the milk by some thermic process. Professor P Lureboullet (Paris) brought forward a survey of the possibilities of diminishing the risks from cow s milk by a thoroughly planned bygienic scheme by legislation and by municipal and collective measures. He summarized the position in certain countries and stressing especially the difficulties, concluded strongly in favor of pasteurisation of milk under proper control as the ideal measure Failing a proper organization, he thought the boiling of milk prior to consumption was the only course. Dr J M Hamill (London), gave a short review of the position in this country as regards bovine tuberculous infection in children. Since, as he pointed out even certified and inherculin tested milk oc casionally contained tubercle bacilli, there was no alternative to some treatment of the milk to destroy organisms. This he thought, was to be found in efficiently controlled pastenrization. He emphatically condemned the idea that the drinking of infected milk was valuable to produce an immunity The discussion was con tinued by Professor F Feer (Zurich) Professor S Monrad (Copenhagen), Professor P Rohmer (Strasbourg) Professor G Frontali (Padua) Dr H. Bock (Berlin) Dr W O Davison (U S A ) Dr H. P Wright (Montreal) Dr J Duzar (Pecs) Professor G Mouriquand (Lyons) Professor G Noeggerath (Freiburg) Dr W Spolverini (Rome) Professor W I. Jundell (Stockholm) and Dr G Petranzi (Hun

The afternoon sessions on the first two days and the morning session on the last day were devoted to short communications given in sectional meetings. On the social side the delegates were offered an excellent series of gatherings. On Thursday

Seriously, one comes to wonder at times just how many of the things that we have introduced into the child's life are real necessities, or actual improvements over the good old ways, and one might well ask oneself just how much chance there is, in the family that can afford all the frills, for the child to have what might be called a natural development. Or are our children really better for having the years once given over to irresponsible play all cut to pattern?

There is a large class of well to do mothers whose care of their children seems to be governed by fads—fads in doctors, fads in schools, fads in foods, in other words, the baby is becoming a fad, and in this day of fads it's not surprising. The writer sometimes thinks that he would like to initiate a new fad whose slogan should be "Give the poor kid a chance".



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# Useful Accidents

Before the world knew anything about germs of disease, we made Pet Milk by concentrating the fresh milk and heating it in sealed cans to make it keep 'When the germ disease relation was discovered, Pet Milk was free from germs

When Pet Milk was first sterilized to 'make it keep" we didn't know anything about the hard curds of cow's milk. It was later discovered that the sterilization made the curds as soft and flocculent as those of human milk.

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# How Clear to a Doctor Is the Madness of War

He Devotes His Time to Saving Life
Then Sees 16,000,000 Die in One Holocaust

OW futile seem a physician's efforts in view of the world's madness. Working always for humanity's welfare he observes all he has conserved swept away in periodic outbursts of group insanity. Doctors must indeed be inclined to agree with Bernard Shaw's conclusion that the earth is the madhouse of the universe.

What a senseless thing is War! What a futile thing! What a brutally insane orgy of wiless killing! It's murder if one man does it. It's heroism if a thousand do War makes widows of wives mourners of mothers, orphans of children. It leaves a trail of Disease, Famine Mutilation and Death It is the supreme evil of human history—the arch enemy of human progress. It destroys our finest manhood, forcing us to breed from debased stock. It imposes a crushing tax burden and impoverishes the world. It indorses mass murder and makes a mockery of every religion on earth.

No one can win a great war Both victor and vanquished pay the bill Every economist concedes that the World War was a major factor in the present depression. It cost 333 billion dollars in direct expense. Seventy-five cents out of every federal tax dollar goes for war

#### Can War Be Downed? Yes, but only through Organized Effort

If we done crush war-war will crush us. We believe it

can be eradicated, just as has been slavery, dueling, wich-burning, religious wars, human sacrifice and a thousand and one obsolete savageries. But we've got to make an effort As Major General John F O'Rvan said, "We must wage Peace"

A machinery for Peace exists, the League of Nations and the World Court The League stopped war between Finland and Sweden, Bulgaria and Greece, Albania and Servia Since its foundation in 1922 the World Court has rendered 19 judgments on issues which would otherwise have threat ened World Peace

Why doesn't the machinery work better? Why didn't the Leagues prevent war between Japan and China? Mary Woolley said, upon returning from Geneva that public opinion must be mobilized behind the world's governments Newton D Baker said only a few weeks ago that education was the world's one hope of ending war

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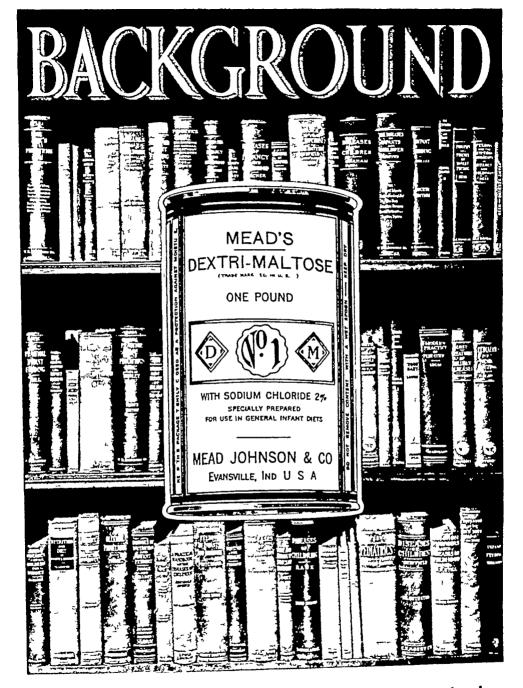
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## The Journal of Pediatrics

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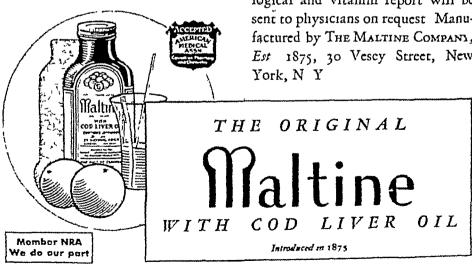
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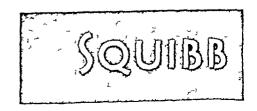
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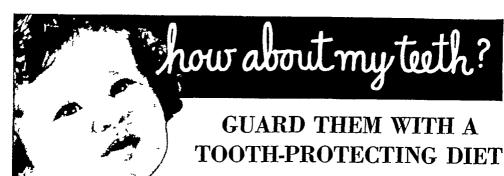
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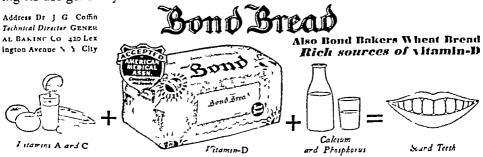
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The prevalence of rickets among children is evidence.

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\* Name of research organization on request



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that even Mrs

\_\_\_ \*can prepare it properly

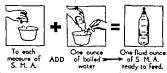
#### SO SIMPLE

much worry and trouble

In ill thank you for sparing her

( ‡ No doubt you can supply names from your practice )

## ANYONE CAN FOLLOW THESE SIMPLE INSTRUCTIONS



This proportion remains unchanged. As the infant grows older you merely increase the quantity as with breast milk. (See table below.)

#### SUGGESTED FEEDING TABLE

Infent	Total Quantity In 24 Hours In Ounces	No of Feedings	Quantity per Feeding In Ounces
2 days 3 days 4 days 5 days 6 days 7 days	1 to 2½ 2½ to 5 5 to 7½ 7½ to 10 10 to 12½ 12½ to 15	2 to 3 3 to 4 4 to 5 5 to 7 5 to 7 5 to 7	14 to 1 14 to 144 1 to 144 1 to 24 1 to 24 2 to 3
2 weeks 4 weeks 6 weeks	15 to 17 ½ 17 ½ to 20 20 to 22 ½	5 to 7 5 to 7 5 to 7	2 to 3 1/2 2 1/2 to 4 3 to 4 1/2
2 months 2½ months 3 months 4 months 5 months 6 months	25 to 27 ¼ 27 ¼ to 30 30 to 32 ¼ 31 ¼ to 35 32 ¼ to 37 ¼	5 to 6 5 to 6 5 5 5	3 ½ to 5 4 to 5 ½ 5 ½ to 6 6 to 6 ½ 6 ½ to 7 6 ½ to 7 ½
to 1 year 6 to 7 Mos.	At this age		61/2 to 10 mary to edd to the diet

especially spinach

\* These quantities refer to fluid ounces of S. M. A diluted according to directions

#### TIME SCHEDULE

7 feedings: 6 9 12 3 6 9 and once during night.
6 feedings: 6 9, 12 3 6 sand 9 or later
6 feedings: 6 10 2 6 10 and 2
5 feedings 6 10 2 6 and 10 or later
7 feedings 6 9 12 3 and 6 or later

NUMBER OF FEEDINGS IN 24 HOURS

The number of feedings in 24 hours abould fikewise be the same as those allowed breast-fed infants, generally stated not more than sevon and not less than five. However when the infant reaches the age of 6 to 7 mooths it is customary to replace one of the feedings with an 8 ounce meal of farina both soup.

## SAVES PHYSICIAN'S

S. M. A. is simple to prescribe The physician is relieved of exacting detail because he has only to increase the amount of S M. A. (as with breast milk) when in his judgment it becomes necessary. The accompanying chart suggests average amounts.

The physician's time is also saved because the chances are good for excellent results under his skilled supervision.

#### S M. A RESEMBLES BREAST MILK

S M. A. is a food for infants—derived from tuberculin tested cows milk, the fat of which is replaced by animal and vegetable fats in cluding biologically tested cod liver oil with the addition of milk sugar potassium chloride, and salar altogether forming an antirachitic food. When diluted according to directions it is essentially similar to human milk in per centages of protein fat, carbohydrates and ash, in chemical constants of the fat and in physical properties.

#### **ETHICAL OF COURSE**

If babies were all alike, it might not be quite so necessary to have a physician plan and supervise feedings. However from the very beginning every package of S. M. A. has carried these instructions prominently on the label. Use only on order and under impervision of a licensed physician. He will give you instructions."



S M A. CORPORATION CLEVELAND OHIO



# Chere's more than CEIN A TOMATO!



THIS PLUMP TOMATO is bursting with a cargo of nutrients that infants need But—infants can not be fed raw tomato, because of the irritating, indigestible skin and seeds The only way, until comparatively recently, to get rid of the skin and seeds has been to extract the juice and throw away the rest



PRACTICALLY EQUAL to orange juice in Vitamin C value, tomato juice has long played a part of recognized importance in the infant dietary. Its ready availability has commended it to physicians and mothers alike. Here, then, is a glass of tomato juice—very good for babies. But—there is more than juice in a tomato!



WHEN THE JUICE is extracted, more is left behind than skin and seeds Rich tomato solids are lost These solids contain vitamins (A, B, and C) and essential minerals

In \*Gerber's Strained Tomatoes, these valuable elements are saved Only the skin and seeds are removed from choice tomatoes, leaving the solids in a finely subdivided and readily acceptable form Nutritive values are conserved by the Gerber vitamin-retaining process

#### \*A FOOD-NOT A BEVERAGE

Strained Tomatoes Green Beans Beets Vege table Soup Carrots Prunes Peas Spinach 4½-oz cans Strained Cereal 10½-oz. cans 15c

Gerber's Strained Tomatoes are twice as concentrated as a canned tomatoes or tomato juice Sterile water may be added to give the desired di lution. A REQUEST If you have occasion to prescribe this product, please do not refer to it as Gerber's 'Tomato Juice as this may confuse the mother Gerber does not produce a tomato juice for infants There is more than juice in a tomato



9 Strained Foods for Baby



GERBER PRODUCTS COMPANY Fremont Mich  (In Canada Fine Foods of Canada, Ltd., Windsor Ont.)  Please send re:  Reprint of the article The Nutriuse Value of Strained Vegetables in Infant Feeding  Sample can of Gerber's Strained Tomatoes							
Name	- Address						
City	Statt						



IN response to demand by physicians small Caritol capsules are now available in packages containing 25 and 50 each, identified as Smaco 500 Each capsule represents 5 drops of Caritol (0.3% carotene in oil) The liquid form of course, is still available (Smaco 505)

Caritol capsules provide an easy way to measure doses and are especially recommended for individuals who object to drops.

#### FRUIT AND VEGETABLE FORM OF VITAMIN A - NO FISHY TASTE

Carotene is derived from fresh vegetables and thereby represents the form in which most vitamin A is consumed by the human body

#### HELPS BUILD RESISTANCE

Caritol by virtue of its vitamin A activity promotes growth and, as indicated by experimental studies may be an aid toward the establishment of resistance of the body to infections in general.

#### ALSO CAPSULES OF CARITOL WITH VITAMIN D

For patients who object to Cod Liver Oil we offer capsules of Caritol with Vitamin D (Smaco 520) The vitamin D is prepared for thera peutic use by methods (Zucker process) developed at Columbia University These small capsules are offered in boxes of 25 Each capsule is equivalent to 5 drops of the liquid form. Therefore two capsules are equivalent to three teaspoons of good cod liver oil plus any advantages that may be attributed to Carotene itself.

Prescribe capsules of Caritol, plain, or with Vitamin D to help build resistance Easy doses, no fishy taste no bad after-tasts.

# S M A CORPORATION CLEVELAND, OHIO





# Information about Karo Syrup Which Will Interest All Physicians —

# Particularly Pediatrists

In response to numerous requests from physicians, Corn Products Refining Company is pleased to publish the following analytical data about Karo Syrup (Blue Label) which has proved so effective in the feeding of infants

> The following acceptance of Karo (Blue Label) by the committee on foods, appeared in Journal of the American Medical Association, January 23rd, 1932

The product is a mixture of corn syrup with a relatively small amount of refiners'syrup Therefiners'syrup must be acceptable in flavor and color and fulfil the U S Department of Agriculture standard for that product, "Refiners' Syrup, treacle, is the residual liquid product obtained in the process of refining raw sugars, and contains not more than 25 per cent of water and not more than 8 per cent of ash."

The corn syrup is manufactured by hydrolysis of high grade corn starch in dilute hydrocloricacid suspension. The mixture is heated under steam pressure until chemical tests indicate the desired degree of hydrolysis. The resultant mix ture is almost completely neutralized with sodium bicarbonate and filtered through white linen filter cloth, the filtrate is passed through a deep bed of animal charcoal for decolorization and deodorization. The final filtrate, which is water clear and odorless, is concentrated under reduced pressure to a density of 1.38 (20 C 120 C)

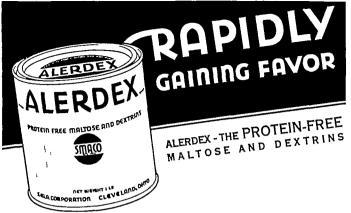
#### CHEMICAL COMPOSITION

		per cent
Moisture		25.3
***		06
Ash	-	
Fat (either extract)		00
Protein (\\ 6.25) -		0.2
Dextrins (by difference)		37 1
Dextring (b) difference)	r ti-di-	
Maltose (method of Wesener and Teller J Indu t.	, tm5m	
Chem 7: 1009 1916)		
Dextrose (method of Wesner and Teller J Indu t	S Engin	
Deathor (managed and and and and and and and and and an		~.5
Chem 7: 1009 1916)		
Surrowe		4.8
		2.3
Invert Sugar		
Titratable acidity a IICI		0 0*5

CORN PRODUCTS REFINING CO.
17 Battery Place New York







#### WHY IS ALERDEX PROTEIN-FREE?

Since certain proteins are frequently the cause of eczemas and other forms of allergy it is desirable to eliminate these offending proteins from the infant diet Cereal proteins are frequently present as contaminants in some milk modifiers The routine use of a protein free carbohydrate in all milk modifications should help to diminish the incidence of these troublesome eczemas. Alerdex is a protein free carbohydrate developed by our Research Division to meet this need and the demand for it is steadily increasing

A modest announcement of Alerdex a year ago found physicians ready and anxious for such a product. There is now a definite trend to use Alerdex routinely in all milk formulas

Of course Alerdex should always be used as the carbohydrate addition with Smaco Hypo Allergic Milks with the assurance that eczemas due to cereal protein sensitization will not be aggravated

#### CHARACTERISTICS OF ALERDEX

- I Helps prevent eczemas when used rout inely due to absence of offending protein.
- 2. Use present formulas because Alerdex has same caloric value and percentage of maltose and dextrina.
- 3 Does not cake on exposure to air because it is non hygroscopic.
- 4. Dissolves readily in warm water or milk.
- 5 Snow white, free flowing powder
- 6 Imempensive—in spite of extra processing under technical control, costs no more.
- O 1921, S.M.A. Corporation, Cleveland, Obio

#### APPROXIMATE ANALYSIS OF ALERDEX

Alerd x is essentially a mixt r of approxim t ly equ 1p rts of maltose and dextrin It is prepared by a new thermally-controlled process of the en symic hydrolysis f pou cereal starch as a result of which it contains n prot in contaminant

Moisture	30
Asb	0.5
F t (ether extract)	0.6
Hydroly ed protein (N x 6.25)	0 05
Reducing s g re as maltose	50.0
Destrin (by difference)	46.0
Level t blespoons, pe ounce	4
Calories per lev 1t blespoon	2734
Calories per ounce	110

Prescribe Alerdex in your own practice For a mples and literatu a simply attach this paragr ph to your letterhead o pre scription blank S, M A Corpor tion 4814 Prospect Avenue, Cleveland, Ohio

50-103

# Souble Rich IN VITAMIN "B"

Ralston Wheat Cereal provides all the food value of finest whole wheat (only coarsest bran removed).

PLUS added quantities of pure wheat germ, which make it richer than any other cereal in the antineuritic, appetite-stimulating vitamin B.

It is a temptingly delicious, satisfying food, equally popular with children and adults.

It cooks in five minutes—costs less than one cent a serving.

Mail the coupon for Research Report on the New Ralston Wheat Cereal and samples for testing.

RALSTON PURINA COMPANY, Dept. I 149 Checkerboard Square, St. Louis, Mo

Please send me copy of your Research Report on the new Raiston Wheat Cereal and samples for testing

Name

Address

This offer limited to residents of the United States



## ALLERGIC IMANIFESTATIONS AND HYPO-ALLERGIC WHOLE MILK



Allereic manifestations caused by food may take any of the following forms

- ECZEMA, especially in infants, caused by ordinary milk.
- GASTRO ENTERIC DISTURB ANCES, as vomiting diarrhea constina
- HYPERACUTE TYPE, with unticaria asthma and symptoms of shock.
- BRONCHIAL ASTHMA.
- URTICARIA.
- ANGIONEUROTIC EDEMA.
- ERYTHEMA MULTIFORME

Where mlik protein is responsible for such disturbances physicians have reported excellent results from the use of Smaco Hypo-Allergic Whole Milk, prepared from tuber culin tested cows milk which is given thermal treatment equivalent to refluxing

Smaco Hypo-Allergic Whole Milk is well tolerated in many cases and can be used in definitely as the processing does not remove any emential food element from the milk the constituent amino acids are still present in the same proportions as before,

The milk thus rendered less allergic is then spray-dried in special equipment and packed in one pound containers in an atmosphere of inert gas (nitrogen) The cost of the powder is 25% less than the liquid form.

#### CHARACTERISTICS of Powdered Hypo-Alleroic Whole Milk (Smaco 302)

Helps prevent eczema in patients hypersen ritive to milk protein.

Can be used indefinitely because all essential food elements of milk are still present.

Use present formulas since this is real cows milk, not a substitute

Individual feedings may be Convenience made up for infants

Lower cost Powder form costs 25% less than Monda

Spray dried in equipment reserved for Hypo-Allergic Milk and Alerdex.

lt keeps. Hermetically scaled in an atmos phere of inert gas

(nitrogen) to prevent deteriors tion.

Developed by the Research Division of S M.A Corpor ation Cleveland Ohio @ 1821



#### A POPULAR PAMPHLET

This twenty two page booklet has proven popular with the medical profession. It contains a brief resume of current timesture on Milk Aberry, conting fifty-one sutherities, prepared especially for Physicians. Bend the coupon for a comptimentary copy of the fifth edition.

#### 5 M. A CORPORATION

CLEVELAND,

[] Trial parings Hypo-Allergic Whole Milk (powder) (For samples and literature without obligation simply attach to prescription blank or letterhead.)

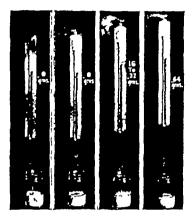
56-102 | Milk Allergy bookist with bibliography

# CURD TENSION

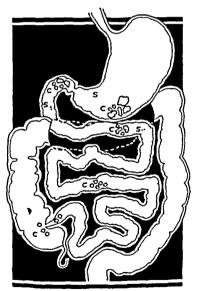
- AND INFANT FEEDING

TS · EFFECT · UPON · THE · ASSIMILATION · OF

### **FATS**



BREAST SIMILAC POWDERED COWS



C—Cows milk S—Similac Schematic drawing of the relative size of the curds of cows milk and Similac vom ited by six weeks old puppies after one half hours ingestion

"AT has a caloric value more than twice that of either carbohydrates or protein and serves very well to make up the necessary energy or caloric requirement. Two of the important vitamins, 'A and 'D', are associated with the fat of milk and when the diet is low in milk fat these vitamins must be supplied in some other form"

"When milk curdles in the infant's stomach it entangles a large proportion of the milk fat in its meshes and only such fat as lies near the surface of the curd can be reached by the digestive juices. The amount of fat in the curd depends upon the amount of fat in the milk"

The soft, fine curds of SIMILAC, which register zero on the tensiometer, expose a greater surface area for the digestion of the fat than do the large, tough curds of fresh cow's milk

The finer the curd the greater the surface area The greater the surface area the more exposed are the fats, carbohydrates, proteins and salts to the digestive enzymes Result a more complete utilization of the food elements

<sup>1</sup> Marriott Infant Nutrition, pg 49

\*Talbot Morse and Talbot, Diseases of Nutrition and In fant feeding, pg 48

Samples and literature will be sent on receipt of your prescription blank

SIMILAC-Made from fresh skim milk (casein modified); with added lactose salts milk fat and vegetable and cod liver oils



DIETETIC LABORATORIES, INC.

# CURD TENSION

- AND INFANT FEEDING -

#### ECT UPON THE ASSIMILATION CARRONTES



BREAST SIMILAC FOWDERED COW'S MILK MILK



C—Cow milk 5—Similes Schematic drawing of the relati its of the cards of cow milk and Similes vomted by six weeks old puppies after onehalf home ingustion.

HE curds of milk contain only a small amount of carbohydrates, sufficient, however to be a disturbing factor in infont feeding.

"A large part of the digestion and absorption of the carbohydrates takes place in the upper part of the small intestines."

"The disaccharides, maliose, sucrose and lactose, are con verted into monosaccharides through the action of enzymes secreted by the small intestine and are absorbed in the form of monosaccharides.

"When absorption is impaired, some sugar may reach the large intestine and here be attacked by the bacteria present. Sugar itself rarely oppears in the stool, it being decomposed to form acids and gases."

The large, tough curds of cow's milk are more slowly disintegrated and thus more slowly release the encased carbohydrates than the soft, flocculent curds of Similac.

The disintegration of the curd of cows milk may not be completed until after the curd, with the encased carbohydrate, has passed that portion of the small intestine where the enzymes for the conversion of dissecharides into monoaccharides are present. There is not this possibility when SIMILAC is fed because the fineness of the curd of SIMILAC does not permit of the encasement of carbohydrates to any extent.

The finer the curd the greater the surface area. The greater the surface area the more exposed are the fats, carbohvdrates, proteins and salts to the digestive enzymes. Result a more complete utilisation of the food elements.

London & Polowrown; Zeitschr f physiol, Chem. 1966, VLIX, 222. Marriett: Infant Nutrillen, pg. 61.

Samples and literature will be sent on receipt of your prescription blank.

SIMILAC-Made from fresh skins mith (exsens medified); with died lactore salts, milk f t and vegetable and end liver affe



DIETETIC

LABORATORIES, INC.,

# "My doctor knows what Mike!"



IT'S probably no news to thousands of doctors-and others concerned with the care of infants-that babies like Clapp foods Just watch a little tot eagerly attacking a Clapp meal and that point is definitely proved

But perhaps some doctors do not know that Clapp's Original Baby Soups and Vegetables are now packed in the new Enamel Purity Pack And that in this packing—the purest that foods can receive—every Clapp item is

selling at a new low q price of 15c a can'

Now you can put the infants in your care on this varied and nourishing diet, which is,



Clapp's Original Baby Soups and Vegetables...also packed in glass jars at former prices



at the same time, a real economy diet

We want you to see and try Clapp foods in this modern new packing Send in the coupon below and we'll forward to you-free of charge-America's largest variety of baby foods

## 15 VARIETIFS

strained)

Baby Soup (Strained) Baby Soup (Un-Vegetable Soup Beef Broth II heatheart Cereal Spinach Carrots Peas Asparagus Beets II ax Tomatoes Beans Prune Pulp

Apple Sauce

Apricot



HAROLD H CLAPP, INC. Dept J 7, 1328 University Ave Rochester, N Y

Pulp

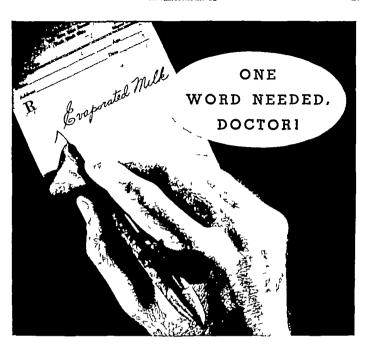
Please send me free of charge a complete assortment — 15 varieties — of Clapp 8 Original Baby Soups and Vegetables in the new Enamel Purity Pack

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OUR Evaporated Milk formula may L be ever so specific as to the ingredi ents, measurements, time of feeding etc. - yet may leave one important decision to the mother and her chance adviser

What brand of Evaporated Milk to use?

You have in mind certain clearly defined standards of quality in Evaporated Milks. But the mother-or her neighborly adviser-has no such standards to guide her In this decision the mother needs your advice.

The Borden Company produces Evaporated Milks in which the physician will find the quality he demands for infant feeding. For seventy five years Borden s has main tained the highest standards of milk selection and the most rigid requirements throughout the process of manufacture. These standards and requirements prevail today in the production of all the Borden brands Borden a Evaporated Milk Pearl Maricopa Oregon St. Charles

Silver Cow All these Borden brands are accepted by the American Medical Association Committee on Foods.

Write for compact, simple infant feeding formulary and scientific literature. Address The Borden Company Dept. 556 350 Med ison Avenue New York, N Y



The Borden Company was the first to submit evaporated milk for acceptance by the Committee on Foods of the American Medical Association, Bor den s was the first evaporated milk to receive the seal of acceptance of this Committee





EVAPORATED MII.K "Irradiated or activated milk possesses a distinct advantage over all other measures of prophylaxis against rickets. It furnishes an automatic means of treatment, one which does not depend upon the co-operation of the mother..."\*

Dr Alfred I Hess in the City of New York Department of Health Quarterly Bulletin, Vol. 1, No. 2, 1933 which states editorially, 'So many inquiries have come to the Department of Health regarding irradiated milk that we have asked Dr. Alfred F. Hess to prepare the following brief article on the subject for our readers.'

# ANY BABY TAKING ITS DAILY RATION OF DRYCO IS THEREBY PROTECTED AGAINST RICKETS'

\*For your convenience Dr. Hess' answer is here given almost in full

The main danger of rickets is that it decreases the resistance and econdly, that it causes deformities especially malformation of the pelvis which in female patients lead to difficulties in childbirth with dan ger to mother and to child Every infant should receive some antirachitic protec tive agent. The latest method which we have at hand is the use of irradiated food products products which have been ren dered active by subjecting them to ultra violet rays. The most significant of the e product is milk Every infant has to de pend upon milk for its nourishment and depends upon it at the very time of life when rickets is rampant in other words during the first year or eighteen months of its existence From this point of view irradiated or activated milk fossesses a distinct a lantage over all other measures ot prophylaxis against rickets. It furni hes an automatic means of treatment one which does not depend upon the co operation of the mother

Dryco is never advertised to the Laity

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# DRYCO

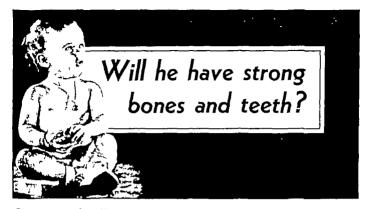
Made from uperior quality milk from which part of the butterfat has been removed irradiated by the ultra violet ray under licene by the Wisconsin Alumni Research Foundation (US Pat No 1680 \$18) and then dried by the lut koller Proce Send for amples and literature

All Dryco, in the hands of druggists
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# The DRY MILK COMPANY, Inc.

205 EAST 42nd STREET DEPT. JP. NEW YORK, N. Y



## So much depends on his mother's diet during pregnancy and lactation

At no time is the need for a protective diet so great as during pregnancy and lactation. All elements required for the

lactation. All elements required for the chill's developing both must come from the mother's food—or from her own body Coconnult has well proved its value during these two periods of special streas. For not only does it substantially in crease the caloic intake it provides extra proteins, carbohydrates, mineral nutrients (food-calcium and food phosphorus) and vitamins.

Prepared according to label directions Cocomait adds 0% more food-energy to mik. Fvery glass a woman drinks is equal in food-energy value to almost free plasses of milk alone

#### Rich in Vitamin D

Highly important to both moth r and child is the rich Vitamin D content of this delicious milk-drink. Cocomalt con child is the rich Vitamin D content or this delicious milk-drink. Cocomait con tains not less than 10 Sternbook (300 ADMA) units of Vitamin D per ounce (under license b. Wisconsin Universit) Alumin Research Founlation) Cocomait comes in powder form easy





Coconait is scientifi food concentrat of sucrose, sk m milk, selected cocoa ba ley malt extract, flavoring ad added Vitami D

ADDS 70% HORE FOOD ENFROY TO MILK (Prepared accord' g t Inhel directions)



to mix with nilk—HOT or COLD at grocery and drug stores in ½ lb. and 1 lb. cans. Also in —lb. cans for hospital use at a special price

#### Free to Physicians

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#### Junior Model

The double row of bristles and the straight handle make the Dr Butler Junior Model toothbrush ideal for children's use

It was specially designed by a dentist and is now prescribed by many leading general practitioners in Dentistry

#### "Single Row" Model

The Dr Butler small "Single Row" toothbrush is indicated for children wearing any form of appliance for regulating teeth, and is recommended by many Orthodontists

As a leading pediatrician you will naturally recognize the worth of both of these brushes

Samples

Samples of each on request. Use the coupon at the right or if you prefer write me on your professional letterhead or simply send your card

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Please send me sample brush as indicated

Junior Model
Single Row Model

Name		 		 	 	-	 **	 	
Address	~		-	 •	 		 	 	



# Forming of Perfect Feet Begins in the Cradle . . . .

Statistics state that 850 of every 1 000 school children suffer from some sort of foot defects. As 98 per cent are born with perfect feet the fault obviously lies in the foot coverings worn during preschool and early school years.

To determine what type of foot coverings are necessary to meet the need of science and develop perfect feet Ideal Baby Shoe Company through its Depart ment of Medical Research and Co-opera tion made a series of studies directed by orthopedic surgeons.

Now we have as sembled in convenient form for ready reference, the results of this and other research

SYNOPSIS OF BABY SHOE RE SEARCH, a Portfolio for Doctors, illustrated with reproductions of X ray studies, contains baby shoe information not available elsewhere, designed to aid the profession in preventing improper foot developments.

This Portfolio will be mailed without obligation to members of the profession who request it on letterhead or prescription blank. Address

Department of Medical Co-operation

MRS DAY'S IDEAL BABY SHOE COMPANY DANVERS MASS

#### Vutamıns A, B, D and G GUARANTEED

THE Committee on Foods of the American Medical Association has taken a commend able stand in the promotion of honest products and of honest advertising by ruling that Vitamin claims shall stipulate the specific vitamin or vitamins present." The Miltine Company concurs in this ruling

Maltine With Cod Liver Oil is a biologically standardized product with a guaranteed potency of vitamins A B D and G When administered with orange or tomato juice vitamin C is supplied. This combination enables physicians to prescribe five important vitamins as a group offering a reliable and beneficial method of building up bodily resistance and bringing about health, normal conditions.

First introduced in 1875 Maltine With Cod Liver Oil has maintained a position of leadership both in quality and in volume. The product is constantly under laboratory supervision to maintain its high quality and to assure the profession that the vitamin A B, D and G content is absolutely guaranteed. Copy of biological and vitamin report will be sent to physicians on request. Manufactured by The Maltine Company.

Est 1875 30 Vesey Street New York N

> Membe VRA We do our part



# The ORIGINAL The ORIGINAL With COD LIVER OIL I load of 1 1875 SHE OTHER HALTINE ADVER THERMING ON DAKE GOVER

# HIGHLIGHTS on Ultraviolet Therapy in Infantile Eczema

"The bactericidal action of the short waves of the water-cooled generator followed by mild and gradually increasing raying to the point of crythema from the air-cooled long wave instrument has given unquestionable results in relieving the acute symptoms and eventual cure of eczema."

> GEORGE E PERCY M D in American Medicine, July 1932

'In infantile eczema generalized exposures for tonic purposes exert pronounced benefit. In adults affected with eczema, ultraviolet therapy is applied for similar purposes and occasionally attains equally notable results, especially in eruptions of internal origin produced by derangements of the calcium metabolism."

"Generalized mercury vapor light treat ments are so efficacious that they should be given in almost every case of infantile exema. On the whole, their value for this condition is not sufficiently recognized. Ultraviolet therapy produces a gradual cessation of the printus and involution of the cruption accompanied by an increase in the elasticity pigmentation and tone of the skin.

GEO CLINTON ANDREWS, A B M D
Diseases of the Skin"
pp 231 and 421 (1931)

It (eczema) is not an external disease or an internal disease. It is both always, and at the same time and often responds to radiation therapy when other remedies fail."

> C M HENRY M D., C.M FAC.S in Can Med Assn Jour, Dec 1931

"This constitutes about one-quarter of all skin diseases. So varied are these that it is impossible to lay down the treatment by ultraviolet radiation with any degree of precision. But when we consider that the underlying pathology of all of them namely either a deficient metabolism on the one-hand or perverted or excess metabolism on the other—and actinotherapy at any rate temporarily alleviates the effects of disordered metabolism—it will be seen that there is sound foundation for its use in eczema."

F H HUMPHRIS M D in Artificial Sunlight and Its Thera peutic Uses (1929) p 171

"In eczema I employ local ultraviolet in a dose sufficient to produce a strong crythema Systemic ultraviolet follows, treatment being given on alternate days."

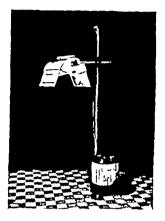
EDWIN L. LEBBERT M D in Physical Therapeutics Nov 1929

'Ultraviolet radiation proves a very valuable therapeutic agent in this com mon condition especially in its subscute and chrome forms.

> ELEANOR H RUSSELL, M D., and W KERR RUSSELL, M D "Ultra Violet Radiation and Acti notherapy"—page 540 (1928)

Our last resort in stubborn and intract able cases of infantile exema is actinotherapy in the form of ultraviolet light and X-ray These marvels of modern physiotherapy have revolutionized der matologic therapeutics and have completely routed the spectre of incurability of exema, so strongly established in the lawman s mind."

Moses Scholtz, M D in Arch of Pediatrics, Oct., 1927



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	15%
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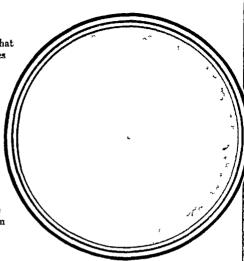
\*"The Vitamins in Health and Disease" by Barnett Sure, Century Co., 1933.

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### Original Communications

SIGNIFICANCE OF THE WATER METABOLISM IN HEALTH
AND DISEASE

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#### INTRODUCTION

WERE we to decorate a map of the Western Hemisphere with pins representing the geographical distribution of individual con tributors to the comparatively scantv literature on the topic of this evening's dissertation it so happens that your own city would be the most densely pegged center before us Because of this fact, I feel twice honored in having been invited to give this year's Packard Memorial lecture on the subject of water metabolism

Unfortunately the breadth of our subject will permit only the most superficial consideration of its many interesting phases. Certain subtopies admittedly of the greatest interest and importance such as those relating to the mechanisms of edema formation and urinary secretions will purposely be given less attention here than they deserve because the readily available medical literature abounds in papers dealing with them. Whereas most treatuses, dealing with the water exchanges of the body direct attention primarily to other aspects of the metabolism and only secondarily to water, it will be my intention to reverse this order in the present discourse, purely for the sake of emphasis

Although the broad science of metabolism had its very beginning in the experimental studies of Sanctorius of Padua (1561 1636) on the

From the Department of Pediatrics, University of Minnesota Minneapolis The Annual Frederick Packard Memorial Lecture. Presented before the Phila d lphia Pediatric Society April 11, 1913

"insensible perspiration," it is obvious to every one acquainted with the subject that progress in the field of water metabolism has lagged far behind that in other branches of physiology. The clinician has indeed long recognized the practical importance of water in certain disease states and has always credited it with a place among the essential constituents of the diet, but appreciation of its true significance in the body economy is only now beginning to manifest itself. That physiologists as a class have likewise failed in the past to give the problems of water metabolism their due recognition is evident from the fact that extensive investigations have not as yet been made with methods comparable to those which have so greatly advanced our knowledge regarding the intermediary metabolism of the proteins, fats, carbohydrates and minerals, and that concerning the vitamins and the total energy exchanges of the body

Yet, if any single constituent of the living organism, or of the food which goes to maintain it, can be said to be the most important, water must be given that distinction, as attested not only by its quantitative position among the major constituents but also by the multiplicity of its essential physiologic rôles Without water there can be no life, and for each organ there appears to be an optimal state of hydration for normal functioning Whereas a mammal, such as the dog or man, may survive for a month or longer without all other food, losing practically his entire glycogen and fat stores and as much as half of his body protein, death may occur if he is deprived of water for longer than a few days, or when he has lost but little more than onefifth of the water incorporated in his tissues When it is remembered that the cells of the body are entirely dependent for their protection against the vicissitudes of the external world upon a delicately adjusted internal environment, characteristically watery in nature, the significance of the statement by Rubner that "the water content of the tissues is anxiously supervised by Nature," can be appreciated As long ago as 1860 Claude Bernard, father of modern physiology, clearly expressed the importance of the fluid matrix when he said, "It is the fixity of the 'milieu interieur' which is the condition of free and independent life" and "all the vital mechanisms, however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment " Cannon quotes Haldane as saying, "No more pregnant sentence was ever framed by a physiologist " We might add, that no more accurate expression of what our ultimate objective in therapeutics should be is likely ever to be made, because homeostasis or constancy of the body processes and materials is synonymous with health. Water is the most important single agent in making such constancy possible

#### THE CHEMICAL NATURE OF WATER

A brief reference to the newer chemistry of water may fittingly be inserted at this point. It is no longer looked upon as being an inert substance consisting entirely of single molecules of  $H_1O$ , but is now thought by Armstrong<sup>2</sup> and others to be a mixture of such simple molecules and polymers of  $H_2O$  groups. According to this view, the higher the temperature the less becomes the degree of polymerization. So that, steam alone is looked upon as being  $H_2O$  while ice is considered to consist of  $(H_2O)_4$  and  $(H_2O)_4$  and liquid water to be a mixture of  $H_2O$ ,  $(H_4O)_2$  and  $(H_1O)_3$ , the relative proportions of each form depending upon the temperature. The smaller open molecules are said to be chemically active, while the larger aggregates with closed groupings are mactive, as indicated in Fig. 1. The recent x-ray diffraction studies of water made by Stewart<sup>4</sup> may require some modifications of this conception of water and the still more recent synthesis of two

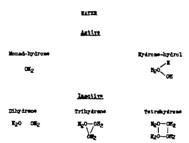


Fig. 1 - Assumed molecular constitution of water

forms of water, heavy and light, by combination of the heavy isotopes of oxygen with the heavy isotopes of hydrogen and the light with the light, promises still further modifications. Nevertheless the peculiar physical properties of water can be explained only on the basis of its being a mixture of molecules of different sizes and degrees of activity with spacial arrangements very different from those originally attributed to it.

#### THE PHYSIOLOGICALLY SUITABLE PROPERTIES OF WATER

This brief description of the chemical constitution of water, and an even more superficial consideration of its physical properties, will suffice to indicate why it is capable of entering into practically all of the regulatory processes of the living body and why nothing can take its place. Its unique thermal properties for instance, make possible the precise regulation of body temperature, its high surface tension serves all processes involving the phenomenon of adsorption, such as

the activity of enzymes, its high dielectric constant makes it a comparatively good insulator, while its matchless capacity as a solvent and ionization medium makes it an ideal vehicle for the transport of all essential materials to and waste products from the fixed cells of the body, as well as a medium for the innumerable chemical reactions which constitute life itself. That water plays more than a passive rôle in the body, however, is indicated by many facts and, as Mathewso points out, "the younger, the more vigorous, the more alive, the more actively growing, the more impressionable cells are, the more watery they are"

#### CONTENT AND DISTRIBUTION IN THE BODY

The percentage water content of the body varies inversely with age in man, as well as in other species The human embryo is 97 5 per cent

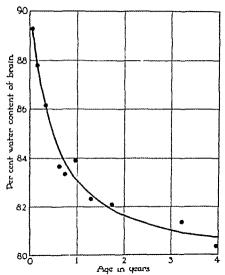


Fig 2 -Relation of water content to age in a representative organ the brain (Mc Ouarrie and Adolph)

water at the sixth week of life At the end of intrauterine life (birth) the percentage of water has decreased to between 71 and 72. Varying somewhat with the amount of fat present, the body of the adult contains between 58 and 65 per cent water. The true relationship of water content to age is best illustrated in a representative organ, like the brain, which shows a diminution in percentage of water with increasing age (Fig. 2). This difference in content undoubtedly explains in part the greater water requirement of infants and their greater susceptibility to the deleterious effects of dehydration. The percentage distribution of the water in the normal human body among the various organs has been shown by Volkmann<sup>7</sup> to be approximately that shown in Table I. In considering the water content from the

TABLE I
DISTRIBUTION OF WATER AMONG THE VARIOUS ORGANS (VOLKMANN)

Muscles	50.8 per cent	Brain 27 per cent
Skeleton	12.5 per cent	Lungs 24 per cent
Skin	66 per cent	Fat 2.8 per cent
Blood	47 per cont	Kidneys 0.6 per cent
Intestines	3.2 per cent	Spleen 04 per cent
Liver	28 per cent	Rest of body 110 per cent

practical point of view, however, it is more convenient to think of it as occurring in several compartments as defined by Gamble. These are distinguished, not only by their situation within or outside the body cells or within closed vessels, but by their composition as well The chief distinction between the intracellular fluid or cell sap which constitutes the major portion of the body s water, and the extracellular fluids (lymph and blood plasma) is the greater concentration of colloids and of potassium and phosphorus compounds in the former and the greater mobility and greater content of sodium and chlorine in the latter. The extracellular or interstitial fluid, which occurs between the fixed cells, on the one hand, and the blood vascular bed on the other, differs in composition from the blood plasma chiefly in its lower content of colloids Under conditions producing either dehydration or oversupply of water, it serves as an adjustable reser voir, which fluctuates in volume according to need. It serves thereby as a buffer depot, particularly for the plasma resembling in this way, to use a simile of Cannon, a swamp, which may be drained during periods of drought but which becomes inundated during times of flood. When large quantities of isotonic NaCl solution were adminis tered to dogs by Engels,° two thirds of that retained was found to be stored in the muscle depots and one sixth in the skin and subcutaneous tissues, showing these to be by far the most important reservoirs for storage of extra water. In all probability the bulk of the salt solu tion temporarily stored in the muscles under these conditions is taken up, not by the muscle cells themselves but by the meshwork of con nective tissue surrounding them

Intracellular water is sometimes referred to as "living water" because it is incorporated in the cell as an essential constituent of the living protoplasm. Death follows its removal just as certainly as it would the removal of the protein or lipid fractions. In considering the significance of water as a constituent of the living organism Gortner. Illustrates this point as follows. In most organisms a very considerable part of the growth process is nothing more or less than an imbibition of the bio-colloids. For example, a frog's egg, weighing on the dry basis only a few milligrams, can after fertilization be placed in a dish of filtered sterile water and allowed to undergo the process of development. Such an egg will undergo cell division, giv

ing rise at the end of several weeks to a living tadpole which may be as much as two centimeters in length and weighing several grams Such a tadpole has never partaken of food other than utilizing the nutrients already present in the original egg and will be found on analysis to contain less dry matter than the original egg, due to the fact that a certain amount of the organic materials present have been utilized as a source of energy and eliminated as carbon dioxide and water The growth during these several weeks has all been due to the intake of water which has become "living water," so the tadpole is actually more than 99 per cent water. It would be ridiculous to speak of this organism as being composed of only 1 per cent of vital materials The water is as much a part of the tadpole as are the fats. proteins, et cetera, which serve to form the gel structure, and the biochemical and biophysical reactions which take place within the cells and tissues of the tadpole are determined probably more by the water which is present than by any or all of the other constituents"

Apparently the greater portion of the water of the body occurs in the free state, that is, in a mobile form which allows it to function as a solvent, as an interactant in chemical processes and as an agent for maintaining body temperature Its location with reference to the body cells is evidently determined chiefly by the forces of osmosis and The remainder occurs either in loose chemical combination with various other constituents or is held fast to the cellular of the circulating colloids by the physical force of imbibition rium between these forms, free \iff bound, is probably involved in cer-For example, Balcar, Woodyatt and Sansum<sup>11</sup> tain vital phenomena have proposed a theory of fever based upon the assumption that a strong shift in the equilibrium toward the "bound" form, when tissue colloids are injured by toxins or other agents, produce a shortage in the supply of free water necessary for dissipation of heat, thus favoring a rise in the body temperature. Much work obviously remains to be done on this interesting phase of the subject before its real significance can be evaluated 12

#### ESSENTIAL ITEMS IN WATER BALANCE

When it is desired to evaluate the total water balance of the body for diagnosis or therapeutic purposes, a complete description can be obtained only by including the items shown in Table II. A fairly complete graphic representation of the total water exchange in a twelve-year-old girl subjected to various procedures influencing the state of hydration of the body is exemplified in Fig. 3, which is largely self-explanatory

It is apparent from any set of data, showing the average values for these individual items, that the gains or losses of metabolic water may be very significant. Particularly is this so in the water balance of young, rapidly growing subjects. A more detailed description of these particular fractions is shown in Table III. It is obvious from the latter data, indicating the extent of participation of water in the growth of tissue, why Kudo<sup>13</sup> and others<sup>14</sup> is have been able to maintain constant body weights in young animals, on otherwise adequate diets, by merely restricting their water intake. It is interesting to note that Kudo ob

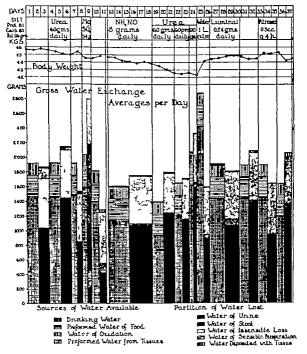


Fig. 1—Graphic representation of separate items in wat r balance of body under various conditions. Constant diet. Thirteen year-old girl. (McQuarrie, Manchester and Hustet)

served an ability on the part of his experimental animals to adapt themselves to a greatly restricted water intake after being on such a regimen for some time. We have often made the same observation in the case of the human subject

The magnitude of the oxidative formation of water within the body cells is shown in Table IV Curiously enough about 12 grams of water

is so formed on the average for each 100 calories, no matter what food is being oxidized. Babcock<sup>16</sup> has suggested that intracellularly formed water probably has greater value for the cell than water from the outside, because it tends to dilute the cell contents and so to draw nutritive substances into the cell by lowering the intracellular osmotic pressure. In the light of Armstrong's theory regarding the nature of water, Cathcart<sup>17</sup> further believes that this endogenous water may represent an active form specially suited for entrance into the metabolic activities of the body, whereas the circulating or "carrier" water may be composed largely of inactive molecules

TABLE II

INDIVIDUAL ITEMS ENTERING INTO COMPUTATION OF THE WATER EXCHANGES OF THE BODY

WATER BALA	NCE OF BODY
SOURCES OF WATER	DISPOSITION OF WATER
1 Water drunk (or injected) 2 Preformed water of food. 3 From oxidations in tissues 4 From syntheses and polymerizations in tissues 5 Released from destruction of body tis	

TABLE III

RELEASE AND CONSUMPTION OF WATER IN THE COURSE OF CELLULAR ACTIVITY

	METABOLI	C	WATER
	AVAILABLE SOURCES		HOW UTILIZED
1	From oxidations in tissues e g C <sub>6</sub> H <sub>12</sub> O <sub>6</sub> + 6O <sub>7</sub> = 6CO <sub>2</sub> + 6H <sub>2</sub> O	1	Combined in hydrolyses. e g R-NH COR + H <sub>2</sub> O = R-NH, + R COOH
	From syntheses in tissues e g R NH <sub>2</sub> + R COOH == R NH COR + H <sub>2</sub> O	2	Deposited with new tissue e g 3 grams H <sub>2</sub> O per 1 gram protein deposited
3	Preformed water from destroyed tis sues e g 3 grams H <sub>2</sub> O per 1 gram protein catabolized.		eg 02 grams H <sub>2</sub> O per 1 gram fat

The quantitative importance of the preformed metabolic water as a source during fasting or marked undernutrition is indicated by the fact that approximately two-thirds of the loss in body weight consists of water. The average amounts of preformed water occurring in some of the common foods are presented in Table V. Water drunk as such or that administered in isotonic solutions merely supplements these primary sources. The approximate amount of extra water needed for the complete metabolism of the food in an ordinary diet is indicated in Table VI.

Examples of the partition of water losses from the body in normal and atrophic infants are given in Table VII It will be seen that un der ordinary conditions approximately two thirds of the output is by way of the kidneys and one third by other pathways Water lost in

TABLE IV

WATER FORMED IN THE OXIDATIVE METABOLISM OF VARIOUS FOODS

	WATER FORMED PER 100 GRAMS	WATER FORMED PEB 100 CALORIES
		e.c.
Pure fat	107 1	11.5
Pure earbohydrate	56 0	13.8
Pure protein	413	10.3
Bread	830	12 9
Potatoes	11.2	12.2
Milk, cow s	8	12.2
Milk, human	87	12.8
Egg yolk	42.3	11.3
Egg white	r 5	11.4
Chicken lenn cooked	15.8	11.2
Beef, medium fat, cooked	24 0	11 0

sensibly by way of the skin and lungs is a factor of the utmost practical significance, not only because of its relative magnitude as an item in the water balance but also because under standard environmental conditions (temperature range between 20° and 24° C and relative

Table \
Water Content of Some Common Foods Used by Infants and Children

FOOD MATERIAL	WATER CONTENT PER CENT BY WEIGHT	WATER CONTENT GM PER 100 CAL
Colostrum	85	119
Human milk	87	180
Cow's milk	87	130
Whole lactic acid milk plus I per cent sugar	82	97
Unaweetened evaporated milk	78	1
40 per cent crenm	<i>1</i> 8	15
Bufter	17	1
Cream cheese	84	82
Egg yolk	49	13
Fgg white	86	156
Veal leg	60	44
Beef sirioin	54	25
Fresh ham	48	17
Fish halibut	75	60
Bread average white	36	14
Zwieback	5	1
Bananas	75	74
Potatoes	63	96
Spinach	83	220
Tomatoes	94	430
Carrots or beets	87	187
Orange	80	163
Apple	63	132

humidity between 30 and 60 per cent) and under circumstances not requiring strenuous muscular activity, approximately one-fourth of the heat produced in the body is dissipated in the process of its vaporization, as first shown by Soderstrom and DuBois <sup>18</sup> On the basis of the latter fact, a fairly accurate gravimetric method for predicting the total heat production of the body has been developed by Benedict and Root<sup>19</sup> and further elaborated by Johnston and Newburg<sup>20</sup> and by Levine and his coworkers <sup>21</sup> Correspondence between the average insensible loss (insensible loss — insensible water + CO<sub>2</sub> exhaled – O<sub>2</sub>

TABLE VI

GRAMS OF WATER NEEDED FOR COMPLETE METABOLISM OF 100 CALORIES OF SOME
FOOD SUBSTANCES

	PREFORMED WATER	GAINED BY OXIDATION	LOST IN DISSIPATING HEAT	LOST IN EXCRETING END PRODUCTS	DEFICIT
Protein	0	10 3	60	300	350
Starch	0	139	60	0	46
Fat	0	11 9	60	0	48
beef, sirloin	25	11 3	60	119	143
Fish, cod	120	104	60	382	312
Eggs, hen	47	11 1	60	154	156
Mılk, whole	127	12 5	60	123	43
Bread	14	13 2	60	69	102
Apples	150	13 9	60	56	-48

Table VII

Partition of Water Output in Infants Under Hospital Conditions in Per
Cent of Total

URINE PER CENT	SKIN AND LUNGS PER CENT	FECES PER CENT	REFERENCE
60 0	J3 5	6 5	Breast fed (Rubner)
63 9	20 5	15 6	Atrophic (Rubner)
71 7	25 9	24	Bottle-fed (Niemann)
75 2	22 6	22	Atrophic (Bahrdt)

simultaneously inhaled) per hour and the total heat production per 24-hour period is sufficiently close to make possible reliable predictions from standard tables. An increase of one gram of insensible loss per hour is equivalent to approximately 32 calories in the 24 hours (Table VIII). In our own work we have found that the state of hydration of the body may influence the insensible water loss without significantly altering the total heat production, dehydration diminishing and superhydration increasing the output <sup>22</sup> (See Table IX, Fig. 4)

The percentage of the total body heat, which is dissipated by vaporization of water, rises rapidly with increasing environmental temperature. This rises from 17 per cent at 15° C to 100 per cent when the environmental temperature equals or goes above that of the body

Barbour<sup>23</sup> has shown that the first response of the body to a rise in the environmental temperature above the critical level for sweating (30° C) is dilution of the blood by water mobilized from the tissues. While it is unlikely that this mechanism is in any way at fault in congenital ichthosis, the absence of sweat glands in severe cases of this disorder greatly limits the ability of such persons to indulge in vigor ous exercise or to withstand high temperatures. They tend to develop fever whenever the need for dissipating extra heat appears. Their insensible perspiration is nevertheless, entirely normal.

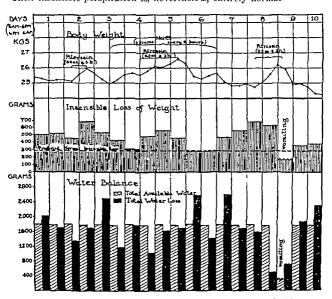


Fig. 4.—Effect of 'superhydration, as produced by forced water drinking and pituitary antillurests, on insensible perspiration. Diet low in protein and minerals Effect of added NaCl Bo, agod nine years wt. 6 kg. (Manchester Husted and McQuarife.)

#### WATER REQUIREMENTS OF THE BODA

The requirements of the body for water can now be estimated fairly closely if all significant conditions are known. They vary with such factors as age muscular activity, temperature and humidity of the surroundings type of diet and of course with the functional state of the various organ systems. The requirement in terms of age and size roughly parallels the total energy metabolism. It is, therefore, several times greater per unit of body weight during infancy than during

TIBLE VIII

TWENT'S FOUR HOUR HEAT PRODUCTION PREDICTED FROM THE HOURLY INSENSIBLE
LOSS OF WEIGHT (MODIFIED FROM BENEDICT AND ROOT)

Insersible loss	PREDICTED HEAT	INSENSIBLE LOSS	PREDICTED HEAT
GRAMS	CALORIES	GRAMS	CALORIES
14 0	900	36 5	1606
$14\ 5$	916	37 0	1622
$15\ 0$	932	37 5	1638
15 5	948	38 0	1655
$16 \ 0$	965	38 5	1670
16.5	981	39 0	1685
17 0	997	39 5	1700
17 5	1012	40 0	1715
18 0	1028	40 5	1730
18 5	1043	41 0	1745
19 0	1059	41 5	1760
19 5	1074	42 0	1775
20 0	1090	42 5	1791
20 5	1106	43 0	1807
21 0	1122	$\overset{\pm 3}{43}\overset{\circ}{5}$	1823
$\frac{21}{5}$	1138	44 0	1840
22 0	1155	44 5	1855
22 5	1170	45 0	1870
23 0	1185	45 5	1885
23 5	1200	46 0	
$\frac{23}{24} \frac{3}{0}$	1215	465	1900
24 5	1231	470	1916
25 O	1247	47 5	1932
25 5	1267	480	1948
26 0	1280	48 5	1965
26 5	1296	49 0	1980
			1995
27 0 27 5	1312	49 5	2010
27 5	1328	50 0	2025
28 0	1345	50 5	2040
28 5	1360	51 0	2055
29 0	1375	51 5	2070
29 5	1390	52 0 50 5	2085
30 0	1407	52 5 53 0	2100
30 5	1421	53 0	2115
31 0	1437	53 5 54 0	2130
31 5	1453	54 0	2145
32 0	1470	54 5 5- 0	2161
32 5	1485	55 0	2177
33 0	1500	55 5	2193
33 5	1517	56 0	2210
34 0	1530	56 5	2226
34 5	1545	57 0	2242
35 0	1560	57 5	2258
<b>35</b> 5	1575	58 0	2275
36 0	1590	58 5	2291

adult life The average amounts of water required by children of different ages under ordinary conditions are shown in Table X

In vigorous muscular exercise the water requirement is raised by about three-fourths of one gram for each large calorie of extra heat so produced. With high environmental temperatures, such as occur in summer or even in winter in overheated nurseries, loss of water by way of the skin may double or even quadruple the ordinary requirements. From a combination of the two factors, strenuous muscular

# TABLE IX

DITIONE IND IN DESTRICTOR INSENSIBLE PRISPERATION AS ACTUALLY MEASURED AND AS PREDICTED FROM GASOMETRIO METABOLISM MEASURED URENERS COMPARED. J. B., AGED SIXTRES YEARS, WEIGHT 48 KG. (FROM MANGINESTER, HUSTED AND MCQUIRILE) ("OUTPARISON OF VALUES FOR HAAD PRODUCTION AS DETERMINED GASOMETRICALITY AND BY THE INERNIELR LOSS METHOD UNDER NORMAL CON

	1			Ę		70 TO 10	TOTAL CALORIES FUR PERSON (12 HOURS)	riches)	INSEMBI FOR PE	NORTHER PERSPERATION FOR PERSPERATION	AATTON JURS)
DIET (1712 CAL.)	ROOM TEMP O.	PER CENT	BODY WEIGHT KG	CHANGE IN BODY WATER (GM.)	DEGREE OF DELITORATION	DET D (TIBSOT)	PREDICTED PROM INS. LOKS	PER CENTAGE DIPPERENCE	MEASURED	PREDICTED FROM TISSOT	PER CENTAGE DIFFERENCE
Borderfine	240	70	17 41	0	Yough	6.9	657	- 0.3	3.8	327	- 0.3
Vonketogenie	17.0	73	46.55	<b>1</b> 10	Modernto	629	580	0 0	200	315	1.4.7
	230	æ	47 60	+,20	Nono	030	650	+ 5 6	319	310	C: 61
Netogenic	61 FC	3	46.62		Silght	979	430	1 32	110	340	297
	10,01	e5	45.36	-1308	Fairly Marked	999	240	-160	201	331	-24.1
Iligh Protein	.36	89	46 46		Voderate	603	614	-114	293	350	-163
	۵ دا	72	40 Ze		Slight	160	630	06-	303	350	737
	55.5	2	45 43	-1,33	Fairly Marked	100	200	-24.7	202	330	-38 0
	وا خ	Ę	44 53	-2087	Fulrly Marked	65,	518	-210	200	334	-35.0
	23.0	20	43 00	- 572	Fairly Marked	639	508	8,15	213	310	-3,0

TABLE VIII

TWENT'S FOUR HOUR HEAT PRODUCTION PREDICTED FROM THE HOURLY INSENSIBLE LOSS OF WEIGHT (MODIFIED FROM BENEDICT AND ROOT)

INSENSIBLE LOSS GRAMS	PREDICTED HEAT CAI ORIES	INSENSIBLE LOSS GRAMS	PREDICTED HEAT CALORIES
14 0	900	36 5	1606
14 5	916	37 0	1622
15 0	932	37 5	1638
15 5	948	38 0	1655
16 0	965	38 5	1670
165	981	39 0	1685
17 0	997	39 5	1700
17 5	1012	40 0	1715
18 0	1028	40 5	1730
18 5	1043	410	1745
19 0	1059	41 5	1760
19 5	1074	42 0	1775
200	1074	42 5	1791
	1106	43 0	1807
$\begin{array}{c} 20\ 5 \\ 21\ 0 \end{array}$	$\frac{1100}{1122}$	43 5	1823
	1132	44 0	1840
21 5		44.5	1855
22 0	1155	44 5 45 0	1870
22 5	1170		
23 0	1185	45 5	1885
23 5	1200	46 0	1900
24 0	1215	46 5	1916
24 5	1231	47 0	1932
25 0	1247	47 5	1948
25 5	1263	48 0	1965
26 0	1280	48 5	1980
26 5	1296	49 0	1995
27 0	1312	49 5	2010
27.5	1328	50 0	2025
28 0	1345	50 5	2040
$28 \ 5$	1360	51 0	2055
$29\ 0$	1375	51 5	2070
$29\ 5$	1390	52 0	2085
30 0	1405	52 5	2100
$30 \ 5$	1421	53 0	2115
31 0	1437	53 5	2130
31 5	1453	54 0	2147
32 0	1470	54 5	2161
32.5	1485	55 0	2177
33 0	1500	55 5 54 3	2193
33 5	1515	56 0	2210
34 0	1530	56 7	2226
34 5	1545	57 0	2242
35 0	1560	57 5	2258
35 5	1575	58 0	2275
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total daily water exchange of between seven and eight kilograms and gives the history of having passed as much as four gallons or about 16 kilograms of urme in one day although his present body weight is only 11 kilograms. The mechanism of this disorder is discussed at greater length below

Adolph<sup>22</sup> has summarized the coefficients for calculating the water requirements of an essentially normal individual in e.e. per 24 hours, from the surface area of the body (in sq. m.) and the total caloric

TABLE A

RANGE OF AVERAGE WATER REQUIREMENT OF CHILDREN AT DIFFERENT AGES UNDER ORDINARY CONDITIONS

AGE		AVERAGE BODY WEIGHT IN KILOS	TOTAL WATER IN 24 HOURS	WATER PER KILO DODY WEIGHT IN 24 HOURS
3 de	1YS	30	240-300	80-100
10 da	.ys	3.2	400-480	125-150
3 m	onths	54	750-964	140-160
6 m	onths	7.3	930-1 186	130-155
9 m	onths	8 6	1 075-1,240	125-145
1 70	er	Ωr	1,140-1 300	120-185
2 ye	enrs	118	1,850-1 475	115-125
4 70		16.2	1 600-1 800	100-110
0 50		20 0	1 800-2 000	90-100
10 7		28 7	2 000-2 440	70-85
14 ye	cars	45 0	2,250-2 700	10-60
18 🕶		54 0	2,160-2 700	40-50

TABLE XI

AVERAGE RATES OF SECRETION OF DIGESTIVE FLUIDS IN ADULT MAN (ROWNTHEE)

SECRETIONS	AMOUNT C.C.	AUTHORITY
Anliva	1500	Bidder and Schmidt
Gastric juice	2000 to 3000	Bidder and Sehmidt
Bile	300 to 500	Pfaff and Balch
Pancrentic juice	500 to 800	Wohlgemuth
Succus interious	8000	Pregl
Approximate Total	8000	•

requirements (in large cal) as shown in Table XII. While this is obviously not a precise practical method it serves to emphasize the approximate magnitudes and the range of variations in the requirements.

#### REGULATION OF WATER CONTENT AND EXCHANGES

Fortunately the body has more or less automatic mechanisms for maintaining an optimum content of tissue water. Thirst, which is apparently a sensation dependent upon some degree of deficit in the free water of the salivary glands and mucous membranes of the mouth. It is usually a trustworthy indicator of the body's need for water. Little concern need be felt regarding the possibility of a per son's taking too much water excepting in a very limited number of

pathological states which will be referred to later. Extra water taken, if unaccompanied by sodium chloride in or near isotonic concentration, is fairly promptly excreted by the kidneys with but little effect upon the general body metabolism. While the mechanism of this water diures is not perfectly understood, Marx<sup>30</sup> claims that the blood is diluted shortly after water is drunk, and to almost the same extent whether the amount taken is 1000, 500 or as little as 50 c.c. Because of the latter fact he assumes that the intake of water starts a complicated chain of reactions between the blood and the tissues, involving the whole mechanism of water metabolism and finally resulting in diures of the excess water. That dilution of the blood results in the calling into activity of an increased number of renal glomeruli is indicated by the work of Richards<sup>31</sup>. The influence of a nervous or

TABLE XII

COEFFICIENTS FOR CALCULATING THE WATER REQUIREMENT OF AN INDIVIDUAL, IN C.C.

PFR 24 HOURS, FROM THE SURFACE AREA OF THE BODY (A) AND THE

CALORIC REQUIREMENT (E)

Growth	0	15 A	30 A
Basal urinary	400 A	1,000 A	1,500 A
Basal fecal	30 A	90 A	150 A
Basal extrarenal	250 A	390 A or	
Exercise (swent)	173 × 04 E	173 × 025 E basal 173 × 055 E exercise	
Temperature (sweat)	~~~~~	1,800 A (C -32)	
Total(approximate)		3,400	5,000

psychic factor has also been demonstrated by Bykow and Berkman<sup>32</sup> and by Marx,<sup>33</sup> who found that blood dilution occurred in trained dogs through the mechanism of conditioned reflexes without the administration of extra water and in a hypnotized man following mere suggestion of water drinking <sup>34</sup> When isotonic NaCl solution is taken instead of water, there is but slight diuresis and blood dilution persists longer. Comparatively enormous amounts of water may be stored in the extracellular reservoirs of the body without harm, if it is given in the form of Ringer's solution.

Administration of excessive amounts of tap water (50 c c per kg per hour) to normal animals was found by Rowntree and his coworkers<sup>3</sup> to produce a symptom complex which they designate as "water intoxication". This syndrome consists of restlessness, muscle tremors, vomiting, diarrhea, incoordination, prostration, generalized convulsions and finally death, if water administration is continued. These signs are much less severe or do not develop at all, however, if physiological saline solution is given instead of tap water. Snell and Rowntree<sup>36</sup> described the case of a man with severe diabetes insipidus with compulsion thirst, who developed these symptoms spontaneously on

several occasions when he drank enormous quantities of tap water (20 quarts in twenty four hours) In collaboration with Thompson and Johnson, the author has recently had the opportunity to study the water and mineral balances in a child with diabetes insimidus who repeatedly had convulsions when a small excess of water was stored fol lowing pitressin administration. Miller and Williams produced as thenia muscle cramps, headache dizziness and elevated blood pres sure, but no convulsions, in a human subject when they administered 10 quarts of water directly into the duodenum by Rehfuss tube body weight of this subject was increased from 124 to 142 pounds in a period of twelve hours Harding and Harris's found 10 per cent NaCl to be the most efficient antidote for 'water intoxication' Rountrees attributes the symptoms to a disturbance of the normal balance be tween the various electrolytes of body fluids Smyth and coworkers to from a more recent study of the mechanism involved, conclude that the essential cause of the convulsions is alkalosis due to loss of gastric Cl

According to the investigations of Lamson and Roca<sup>41</sup> and of Pick<sup>42</sup> and his coworkers the sequence of events resulting from the liberal administration of fluid in the normal subject is as follows. The liver acts as a temporary reservoir for a considerable portion of the excess water taken thus preventing sudden overloading of the right side of the heart. The liver then diminishes in size gradually as the stored fluid escapes into the general circulation by way of the lymphatics. In the normal dog diuresis from water ingestion was found by Molitor and Pick<sup>42</sup> to begin not earlier than 50 to 60 minutes after water was given and lasted for three or four hours, while in the dog with an Eck fistula (which largely excludes the liver from the circulation) extra water began to appear in the urine within 20 to 30 minutes and the diuresis required but half the normal time for its completion

The mechanism by which the liver performs this function as a tem porary reservoir is apparently as follows. Through the reflex activity of the sympathetic vasometer system (as confirmed by adrenalin in jections) constriction of the hepatic veins and closing of their valves follows the ingestion of the fluid, thus causing partial obstruction to the outflow from the liver. Simultaneously with this the pressure in both the hepatic artery and the portal veins increases causing thereby increased filtration pressure in the liver capillaries with gradual outflow of water into the lymph spaces and finally into the thoracic duet Excess water taken as such is then fairly promptly exercted by the kidneys whereas isotonic NaCl solution is secondarily stored for a longer time in the extracellular depots of the body particularly in the muscles and skin as previously pointed out. In liver disease this tem porary storage function is said to be impaired as indicated by greater dilution of the blood following water administration.

#### INTERCHANGE OF WATER THROUGH LIVING MEMBRANES

Revolving around the problem of edema, much study has been devoted in recent years to the mechanism of interchange of fluid between the blood capillaties, on the one hand, and the lymph or tissue spaces (intercellular reservoir), on the other Since the subject has been adequately summarized in recent papers by Leiter,43 Landis44 and others, however, little need be said of it here excepting to enumerate the chief factors concerned Starling's original claim, that the outflow of fluid from the capillaries is dependent upon the hydrostatic pressure of the blood within them and that the inflow from the tissues is dependent upon the colloidal osmotic pressure of the plasma, has been adequately substantiated, i.e., when the hydrostatic pressure at the venous end of the capillaries is greater than the osmotic pressure of the plasma proteins, edema will occur Colloidal osmotic pressures below 19 to 20 mm of mercury,40 corresponding with a total plasma protein range below  $5.5 \pm 0.3$  per cent or a plasma albumin range below 25 ± 03 per cent or plasma specific gravity below 1022,47 favor the occurrence of edema As pointed out by Landis and others, there are undoubtedly additional factors of importance, particularly under abnormal conditions Chief among these factors are tissue pressure. amount of protein which has escaped into the fluid outside of the capillaries, local temperature and state of oxygenation of the blood Injury of any kind to the capillary walls results in increased permeability not only to water and simple crystalloids but to plasma proteins and hpids as well Many of these factors are undoubtedly involved also in the passage of fluids through the epithelial as well as the endo thelial cells in the special organs, such as the kidneys, the cerebrospinal system, the gastrointestinal tract and various purely secretory structures, but much still remains to be learned regarding the exact mechanisms of transfer in these complicated systems

The factors regulating exchange of water between the intracellular and the extracellular compartments have not been studied extensively, although they are undoubtedly of the utmost importance to the organism. In addition to certain of those enumerated above, there are unquestionably others to be considered, such as the different mineral patterns of the fluids on the two sides of the cell membrane, the acid base equilibrium, the type of metabolic process predominating within the cells, the physicochemical peculiarities of the cell colloids and membranes, and lastly certain extrinsic nervous and endocrine factors. Considered in this light, it is obvious that cellular activity must be accompanied by continuous changes in the water distribution between the cells and their immediate environment.

#### EFFECTS OF VARIOUS IONS

While any shift in the acid base equilibrium of the body fluids toward the alkaline side appears to favor the retention of water by the tis sues,48 the Na 10n, in contrast with all others, appears to be more or less specifically active in this regard. While Br behaves very similarly to Cl, attempts to replace Na by other cations, as for instance K, usu ally results in water loss rather than storage. A shift of the acid base balance toward the acid side results in loss of body water. The action of mineral acids and acid forming salts, such as NH,Cl, CaCl, and NH, NO, is similar to that of the ketogenic type of acidosis and the acidosis of severe diarrhea, in causing a loss of body water. While mercase in the H ion concentration per sc may be important because of its direct influence on the capacity of the colloids to hold water the loss of Na which occurs under such conditions is probably the more potent factor Fenn's has recently found that K migrates into or from muscle cells in company with OH and not with other amons Potassium, therefore tends to shift from an intracellular to an extra cellular position when the OH concentration within the cell is greater than that in the fluids outside of the cell. The direction is reversed when the pH of the extracellular medium is higher than that of the cell fluid Presumably water translocation accompanies such shifts Haldı and his coworkers on a study of the factors affecting hydration of nervous tissue in vitro found that different parts of the brain swell to a certain degree when placed in distilled water. They then found that the amons of various K salts inhibit water absorption by the tis sues in the following order citrate> tartrate> oxalate> 80.> ace tate > CNS > Br > NO > Cl > I In the cation series the bivalent ions were found to inhibit swelling more effectively than monovalent ions The cations of CI inhibited the taking up of water as follows Ca, Ba, Sr> Na Li> K Ca Rb

#### INPLUENCE OF DIET

Beyond the facts first that a minimum amount of water is required for the excretion of the nonvolatile end products of catabolism (100 cc for every 45 grams urea and 65 c.c for each gram of ash), second that prolonged protein deficiency causes water retention secondary to the lowering of the plasma protein content and third, that ketogenesis promotes loss of body water, as already indicated the dietary has but little influence on water regulation. The claim that carbohydrate per so has a specific water retaining effect has not to my knowledge, been adequately substantiated by uncomplicated experimentation. The impression, that a high carbohydrate diet results in storage of excess water in the tissues probably originated from observations made on so-called hydrolable infants and older subjects suffering from genuine

nutritional edema. It has been well established that the vast majority of such patients retain water because of the low plasma protein which results from a deficiency of protein in the diet. It is probably true that the edema found in the "moist" type of beliber is explainable on the same basis <sup>51</sup>. Of course, carbohydrate has a specific effect in checking the excessive water loss due to the ketogenic type of acidosis merely by virtue of its effect in counteracting ketogenesis.

#### RÔLE OF PHOSPHOLIPIDS AND CHOLESTEROL

That the balance in the tissues between the physiologically antagonistic substances, cholesterol and lecithin, may be an important factor in water metabolism is indicated, not only by the fact that the former is lyophobic and the latter lyophilic, but even more directly, by the finding of Degkwitz52 that cholesterol administered parenterally results in active diuresis while lecithin causes water retention Dahmlos and Soléss found that lecithin and OH- together favor an oil in water dispersion system, while cholesterol and H+ are antagonistic to the formation of such a system They, therefore, conclude that lipids constitute a very important factor in the penetrability of membranes by water and electrolytes Cholesterol injected intravenously was found by these authors also to cause temporary hydremia and an increase in plasma Cl which resulted later in an increased output of both water and Cl in the urine Lecithin is reported to have had an opposite effect In this connection it is interesting to note that Haustein<sup>54</sup> found the serum cholesterol to be low in a series of hydrolabile children

#### ENDOCRINE AND NERVOUS FACTORS

The most important extrinsic factors in the regulation of the water metabolism are the interrelated endocrine and nervous influences the former, the secretion from the posterior lobe and pars intermedia of the pituitary body is unquestionably the most potent. This was first discovered in 1901 by Magnus and Schafer,55 who found it to have a diuretic action when injected into the anesthetized animal Not until 12 years later was its more important antidiuretic action in the unnarcotized subject discovered by von den Velden 66 In a heart-lungkidney preparation made in such a way that the pituitary body could be inserted at will, Starling and Verney<sup>57</sup> found that the effect of its presence in the circuit was to interrupt the flow of urine They observed in a similar preparation that the antidiuretic activity following pituitary extract was accompanied by an increased chloride excretion 58 Motzfeldt59 first proved its antidiuretic effect during polyuria due to oral administration of large quantities of water, while von den Velden demonstrated its effectiveness in stemming the flow of urine in diabetes insipidus when injected subcutaneously Blumgart 10 later found that it is just as efficient in controlling the polyuria of diabetes

insipidus when sprayed intranasally as when given by hypodermic in jection. In a special study on the diphasic action of pituitrin McFar lane<sup>61</sup> found that high speed intravenous injection, like light ether anesthesia, tends to favor a diuretic response, while slow intravenous injection inhibits urmary flow.

McQuarrie and Peelers: made the observation that there is a significant net loss in body weight following a period of sustained pitulitary antidiuresis when the subject is on a low mineral, high water intake. Thompson, Ziegler and McQuarries have found this procedure to be effective in reducing certain types of edema. In several instances the equivalent of the well known 'spontaneous diuresis' has apparently been initiated by the procedure when the level of the serum proteins at the time of the test was not far below the critical point for edema formation. This weight reducing effect is apparently dependent upon the extra exerction of salt during the period of antidiuresis

The mechanism by which this hormone produces antidiuresis is still the subject of controversy, some workers believing that it acts directly on the renal mechanism, others that it affects the other tissues of the body primarily The latter observers consider that the kidneys func tion in a purely secondary manner in response to changes in the blood circulating through them It seems highly probable that the action is a complicated one involving both the kidneys and the general body tissues simultaneously. Richards and Plant found by direct observa tion that the first response to the extract was constriction of the ef ferent glomerular vessels, which produced a temporary diuresis while a later more striking response was constriction of the afferent vessels which resulted in antidiuresis According to Geiling 65 increased reab sorption from the kidney tubules resulting from a specific effect of infundibular extract on the tubular epithelium may be largely re sponsible for the antidiuresis Marshalls has recently obtained con vincing evidence that the loop of Henle may be the chief site of anti diuretic action in the kidney Exerction of potassium chloride urea and other substances given by mouth with one liter of water was found by Adolph and Ericson not to be inhibited by intramuscular injections of pituitrin These authors found that the amount of water ex creted under these conditions was limited to that for removing the excess salt the remainder being retained. They concluded that the extract acts by rendering the kidneys insensitive to excess water in the blood plasma

That pituitrin affects other tissues as well as the kidneys is indicated by the finding that salivary gastric and intestinal secretions are in hibited by its injection <sup>5, 63</sup>. At the same time lymph flow decreases and its protein content increases Hydremia and mobilization of electrolytes from the tissues into the blood stream occur following injection of pituitary extract, even after bilateral nephrectom. <sup>56</sup> Stelle <sup>76</sup>

finding an increased urinary excretion of valious salts during antidiuresis, concluded that the effect of pituitrin is to mobilize electrolytes into the blood and in so doing renders the tissues capable of taking up more water On the basis of this, he advances the theory that in diabetes insipidus the failure of the body to retain water is due to a reversal of the electrolytic conditions found in the tissues when pituitary extract is administered Baiboui and his associates71 found an increase in the water content of the cerebrum, medulla and basal gangha and in the muscles and hver, following pitressin injection, whereas they found a decrease in the skin and subcutaneous tissues From water vapor studies by Hill's method, it was found by Barbour that water administration tended to produce less of an osmotic pressure fall after pituitary extract than it did in the absence of this substance Yet the blood specific gravity fall was decidedly greater author interprets this as an indication that the pituitary hormone causes mobilization into the blood of a slightly hypertonic salt solu-He concludes that the kidney is tending to assume a minor rôle as a primary locus of water shifting after pituitary administration

Glass, 72 who likewise found the water content of striated muscle markedly increased by injection of pituitary extract, considered this control of tissue swelling by pituitrin to be dependent upon nerve action because sympathectomy as well as extirpation of the centers of the midbrain markedly affected the water content of the muscles. Hypertonic solutions interfere with the hypophyseal influence on tissue swelling by preventing escape of plasma water to the tissues. According to Janssen, 73 section of the spinal cord at the level of the fifth cervical interspace does not interfere with the action of posterior pituitary extract. Hoff and Potzl 74 obtained contrary results. Ochme and Ochme 5 found the extract to exert its antidiuretic effect after complete degeneration of the renal nerves. In clinical hyperpituitary disease Marx 76 finds that water ingestion causes a long-lasting hydremia, while in hypopituitary disorders anhydremia may result from a simple Volhard water-drinking test

It has been established by the recent work of Pines<sup>77</sup> and Greving<sup>78</sup> that the pars intermedia and the posterior lobe of the pituitary gland are under central nervous control through fibers originating in the nucleus supraopticus and possibly nucleus paraventricularis. Apparently it is injury to this tract of fibers or their central nuclei which causes the marked polyunia, demonstrated by Camus and Roussy, Ashner<sup>80</sup> and Bailey and Bremer<sup>81</sup> to follow puncture in that region Houssay and Hug<sup>82</sup> found the polyunia in this experimental form of diabetes insipidus to be primary and not dependent upon polydypsia, glycosuria or increase in blood pressure. Denervation of both kidneys prior to puncture in the region of the hypothalamus, according to them, does not prevent the polyuna. The latter is controlled, however,

by subcutaneous or intranasal administration of posterior pituitary extract. Clinical diabetes insipidus due to tumor growth or to an in flammatory lesion involving the region of the tuber cinereum or hypothalamus, resembles this experimental form in every way.

Cushing and Goetsch<sup>82</sup> were the first to identify posterior pituitary secretion in the eysternal and ventricular fluids. They did not find it, however, in the spinal subarachnoid spaces Hoff and Wermerst found that either strong emotional stimuli or administration of diuretics leads to an increase in the amount present in the cerebrospinal fluid Karplus and Peczenik\* demonstrated a similar response to electrical stimulation of the tuber cinereum. Hoff and Wermer interpret the response to administration of diffreties as a compensatory reaction on the part of the body to prevent excessive loss of water Cushing 46 has more recently discovered that direct introduction of pitressin into the third ventricle in man causes a typical parasympathetic, or pilocarpin like, response with flushing of the skin and visible sweating, while in tramuscular or subcutaneous injection, of course produces a typical sympathetic reaction. The spinal anesthetic avertin, and atropine both prevent the parasympathetic response from intraventricular ad ministration. This newer work on the action of the pituitary secretion and the vegetative centers in the diencephalon serves to emphasize still further the fact that the neuroendocrine mechanism plays a predominating rôle in the regulation of the water metabolism

The extreme polyuria of experimental or clinical diabetes insipidus has long suggested the elaboration in the body of diuretic hormones which are normally balanced by the antidiuretic pituitary secretion Bourgumer and Ohvetes have both reported the presence of a strongly diuretic extract from the diencephalon Bourguin obtained such a diuretic principle from the region of the mammillary bodies, but not elsewhere in the brain in dogs with experimental diabetes insipidus She found the same substance in the blood and urine of these dogs but not in normal animals Trendelenburg " using slightly different technic, failed to confirm these findings Teel% reported finding a markedly diuretic substance in an extract from the anterior lobe of the pituitary body To my knowledge this has not as yet been con firmed by other workers. The observation of Hann \*1 however is of special interest in this connection. He demonstrated that polyuma ceased terminally in cases of diabetes insipidus due to lesions of the posterior lobe of the hypophysis when the lesion gradually encroached upon and destroyed the anterior lobe

Pick 43 Glaubach and Molitor 03 Porges 32 and Grossman 34 have all reported the presence of a strongly diuretic principle in the liver, ad ministration of which is said by Pick to be effective in certain cases of nephrosis and in uremia from experimental reduction of kidney substance. Ivy 36 has demonstrated that secretin has a mildly diuretic

effect Although there is no definite proof of such a relationship, it is barely possible that these substances play a special rôle in water divires

Eppingeror demonstrated the importance of the thyroid hormone in water metabolism, showing it to have a mildly diuretic action Epstein<sup>98</sup> and others have shown that this diuretic effect of thyroxin is due, not to any direct action on the kidneys, but to its mobilizing fluid from the tissues into the blood Pituitrin inhibits the diuresis of thy-In myxedema or cretinism, thyroid extract causes removal of stored water and NaCl from the tissues in a specific manner Ordinary diuretics acting primarily on the kidneys do not remove the excess fluid in such cases. In some types of edema parathyroid extract has been shown by Mason, on Meakins, 100 McCann, 101 Reitzel and Stone, 102 and others to exert a diuretic action We have also seen striking examples of this effect. The observation by Baar 103 of increased water in the brain tissues of subjects with infantile tetany is interesting in this connection This author considers the increased hydration of the brain tissue to be of primary significance in the symptom complex Parathormone, of course, is specific in relieving this type of overhy-Ellis<sup>104</sup> has reported a similar increase in water content of the brain in guanadine tetany, as well as in the tetany of experimental parathyroprevia

Drabkm<sup>105</sup> and others have demonstrated the tissue hydrating effect of insulin and have pointed out the importance of water in the action of insulin on the carbohydrate metabolism. According to Drabkin, insulin convulsions appear to be more closely related to increased hydration of the brain tissue than to the hypoglycemia per se. The retention of fluid which follows administration of insulin in cases of severe diabetes mellitus with dehydration often goes beyond the point of normal rehydration to one of edema formation <sup>100</sup> Schiff and Choremis<sup>107</sup> showed that dehydration decreases the efficiency of carbohydrate metabolism and insulin action. Whether or not an endocrine factor is involved in the water retention associated with obesity is not known. The circulatory factor is probably sufficient to account for the phenomenon in most instances.

That the internal secretion of the adrenal cortex plays an important rôle in the regulation of the fluid balances of the body is indicated by the recent reports of Swingle<sup>108</sup> and coworkers and by Silvette <sup>109</sup> The former found that water enters the tissues from the vascular system at an abnormally rapid rate in adrenalectomized animals, causing the blood volume to shrink and the blood pressure to fall progressively to the death level, unless an extract of the gland is administered. Silvette found that adrenalectomized rats excrete less urine and more chlorides than normal animals under the same fasting conditions. A definitely reduced ability to eliminate injected fluids was found in

animals suffering from cortical insufficiency. The muscles and paren chymatous organs of animals with adrenal insufficiency showed a higher water content than normal, while the blood showed concentration, from which the author concludes that the impaired ability of the kidneys to exerct water is extrarenal in origin.

#### STATE OF HYDRATION AND RESISTANCE TO INFECTION

The relationship of states of hydration to infections, quite apart from that involved in heat loss by vaporization of water during fever is very important Barbour 110 and Underhill 111 have shown that the blood tends to become concentrated early in the course of a febrile illness. In fever dilution of the plasma precedes a fall in temperature from the use of antipyretics according to the work of Barbour Ap parently a similar mobilization of water from the tissues into the blood frequently accompanies the natural termination of fever in the acute infectious diseases Sandelowsky 112 was the first to study the blood concentration, salt balance and weight changes in patients with pneu monia In seven of his eleven cases the body weight either increased or remained stationary during the febrile period but fell rapidly after the crisis The four remaining cases showed a precritical loss of weight. In a study of the total base and chloride metabolism in rela tion to salt and water retention in infants with primary pneumonia, Wilder and Drake113 observed a negative base and chloride balance, when the intake of these ions was low, but a markedly positive bal ance when the intake was high before the crisis. In the former case the base and chloride of the plasma were low and the weight loss was rapid whereas in the latter, those values were normal or elevated and the weight was increased often with visible edema. Rapid excretion of the stored water and salt accounted for the post critical loss in body weight. A direct relationship between the mortality rate and the degree of water retention was suggested by the data. These authors, therefore advise the use of a known NaCl intake (15 cc 0.1 N NaCl solution per pound of body weight in 24 hours) to prevent water retention Sunderman and Austin<sup>114</sup> confirmed these findings as regards water retention in pneumonia and showed definitely that there was a percentile increase in the water content of the tissues during several precritical days While the evidence for water shifting due to infec tion is more spectacular in pneumonia than in most febrile illnesses the same general reaction appears to be common to all diseases of this class and to serum sickness as well 118 That water shifting is involved in the related allergic phenomena is indicated by the experimental studies of Rubin and Kellettiis who found that dehydration has a strongly protective reaction against the harmful effects of anaphylac tic or histamine shock Chronic water logging of the tissues appar ently lowers the resistance to acute infection, as attested by the well

known increase in susceptibility of so-called hydrolabile infants and of patients with nephrosis and chronic cardiac anasarca. Preliminary experiments now being conducted in our clinic by Doctor Ross Weisiger suggest, so far as they go, that the optimum state of hydration for resistance to acute infection may be one of mild dehydration.

#### WATER CONTENT AND FUNCTIONAL ACTIVITY OF NERVOUS TISSUE

The possible relationship between the state of hydration of nervous tissue and increased irritability has already been alluded to in our discussion of "water intolication," tetany and the mechanism of insulin convulsions. From what little evidence is available, it appears to be a rule that the greater the degree of hydration, the more irritable nervous tissue is. Of course, the fact that the various electrolyte equilibria and other factors are often equally important must not be overlocked. It seems probable that the increased ease with which infants and young children have convulsions, as compared with adults, may depend in part upon the significantly greater water content in their brains. Whenever nerve tissue is injuried, it imbibes water and becomes more irritable.

Barbour and his coworkers117 have demonstrated an increase in the water content of the brain produced by withdrawal of morphine from morphine edicted dogs. This increased hydration of the brain tissue is given by them as the cause of the nervous tremors and increased excitability in such subjects Barbour 118 has shown also that ether anesthesia, as well as morphine narcosis, is accompanied by a decrease in the water content of the brain. The brain edema found at autopsy in cases of nephritic unemia status epilepticus and eclampsia in pregnant women is well known The work of Gamble, 110 Fav. 120 the author. 121 and others has demonstrated that a deficit in the body water tends to favor cessation of convulsions in epilepsy, while a positive water balance increases the convulsive tendency That associated disturbances in the mineral balance of the brain cells may be of importance in this connection is indicated by the more recent experimental studies of the author and his coworkers 04 102 Like many of the other problems of water metabolism, however that concerning the precise relationship of tissue hydration to convulsive phenomena is greatly involved and will undoubtedly require far more extensive scientific investigation for its ultimate solution

In the present hurried review we have been able merely to sketch the vague outlines of the field of water metabolism in relationship to clinical medicine. Nevertheless, it may suffice to stimulate additional interest in a comparatively neglected phase of practical physiology, which holds unusual promise for the future investigator.

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it is recalled that successful cases are reported with far more fre quency than those that succumb to the disease with or without opera tion. The careful scrutiny of the reports of a large number of hos pitals for children would be the only basis for a rational deduction

There seems to be little or no available data concerning many features of the etiology, such as the race habits, climate, food or hereditary factors. When one thinks of the great variety of foods used by children of this country, and the contrast in living conditions, it would seem that if diet enters into the cause of ulcer it should be apparent after a careful survey. The reported cases do not suggest such a relation. In these days of the cafeteria and the deheatessen it would seem that ulcer would be the logical result of the indiscriminate barrage to which the gastrointestinal tract is subjected, if food plays any part in the etiology of ulcer. In the absence of any known etiology most writers on this subject believe the cause is the same as in the adult. This seems to be another way of saying we do not know. We can surely eliminate alcohol tobacco and financial worries among the causes in children.

The ulcers have about the same anatomical distribution as in the adult, namely, on the lesser curvature near the pylorus and on the anterior wall of the duodenum. This will apply to 90 per cent of the cases. The ulcers go on to perforation or may heal and obstruct the pylorus by the cicatrix. No case of carcinoma which had its origin in a recognized ulcer has been reported in a child

The symptoms are somewhat vague, except in the cases of perfora tion, and in those cases they have the symptomatology of peritonitis If a careful history is obtained it will be noted in the majority of cases that the child has had some dyspepsia over a period of months. Usu ally the pain has been too mild to attract attention and at other times it has been cramplike. The relation to food and remission of symp toms have not been prominent. It is not unlikely that the appendix has been removed during one of the attacks but without relief of the dyspensia. The outstanding symptom if present, and it is present in 40 per cent of the cases is the vomiting of blood, or blood in the stools. This one symptom means more than all the others combined and as sociated with dyspensia should be the incentive for as thorough an examination as we would give the older patient. Other symptoms which have been noted are vomiting, hunger pain, epigastric pain loss of weight anemia, constination and underdevelopment. These symp toms are so common to childhood that they lose their diagnostic sig nificance Children are so prone to vomit and suffer cramps that these symptoms ordinarily of prime importance in any abdominal complaint in an adult are generally dismissed with a dose of castor oil and an indictment of the previous meal. Only the most painstaking examina

tion can elicit the complaints from an intelligent child that the man or woman would disclose with cheerful garrulity

It is so exceptional that the diagnosis of chronic ulcer is correctly made that one hesitates even to suggest it. One essential is to realize that chronic peptic ulcer in children is possible. With this fact in mind, chronic dyspepsia in a child should certainly excite our sus picions and demand the use of the x-ray. Few roentgenologists are willing to go further in diagnosis of chronic ulcer than to state that an organic lesion is present in the prepyloric region or the duodenum, unless a typical crater is present. Hematemesis or melena, in the absence of a known cause, points strongly to the presence of an ulcer, and with a roentgenogram showing an organic lesion near the pyloris, the diagnosis is almost conclusive

The treatment offers very much and should be medical primarily, unless confronted with a suigical emergency. Too few cases have been reported in which the medical treatment has been checked before and after with the x-ray. The diagnosis could scarcely be in doubt in some cases that have responded promptly to dietary measures and remained well over a period of years. The Sippey treatment has been generally used. Surgery is necessary in the perforation, the pyloric obstruction, and in the case that does not respond to long and careful medical measures. When an operation is demanded, except for perforation, a plastic operation on the pylorus, such as the Mayo, Judd, or Finney should be the one of choice, and the posterior gastroenterostomy reserved for that type in which the former operations are inappropriate or impossible. We wish to report two cases

CASE 1 -Miss D F of North Carolina, fifteen years old, referred by Dr William Gerry Morgan, from whose records these notes were made

Family History—Parents living and well. Two brothers died of accidents Other brothers and sisters (four) in good health

Past History—She has had the milder discuses of childhood. Since the age of six has had "bowel trouble," and at this age had her first hemorrhage from the bowels. She has never been robust since. Her tonsils were removed a year later, and at the age of thirteen an appendectomy was done

Present Illness—Beginning at the age of six, with her first hemorrhage, she has suffered with pain in the region of the gallbladder or pylorus, and constipation has been pronounced. She has been on a diet which contains much roughage, but with out relief to either the pain or constipation. There have been intervals of relief from the pain, and then vomiting and pain would return, lasting periods of three weeks approximately. Since February, 1932, she has had less relief and on seven different occasions macroscopic blood has appeared in the stools.

Physical Examination — Weight 101½ pounds, height 64¼ inches. Skin clear and of good color Respiratory murmur clear and breezy, no rales, expansion good Heart sounds were regular, clear, rate 72 per minute—apex beat not displaced Liver dullness normal. Gallbladder could not be felt and no tenderness elicited.

Abdomen—Pannicus spare, belly flat, spine prominent, splenic duliness normal Old well healed appendiceal scar Abdominal reflexes exaggerated Recti of good tone Only tenderness to be noted is at the site of the appendix scar

Gastric Analysis - Free HCl 56, combined neidity 11 total acidity 66

Blood Examination —R B C. 4,400,000, WB C. 7500 Hg 79, 48 polymorpho nuclears, 46 lymphocytes 4 cosinophiles 1 basophile, 1 large mononuclear Marked achronia. Cong time 214 minutes.

The examination of the urine showed no abnormal constituents and the stool was negative for blood. B.M.R., 12 per cent, 17 per cent, 5 per cent on three different occasions. The x-ray examination is reported as follows

'The chest is negative. The stomach shows marked reduplication of the mucosa The rugae are very prominent throughout the entire stomach and the same condition also causes deformly of the duodenal cap. The appearance is that of a baggy redundant mucosa and strongly suggests polyposis in the duodenum. It is noted that at the 24 hour period the stomach is filled with some opaque material probably some bismuth or other opaque material taken by the patient. The cenum is dilated but is otherwise normal. The entire colon is spastic but shows no other abnormality. There is no ovidence of periapical disease of the teeth. Re-examination one week later of the stomach and duodenum after the administration of belladonna shows the same appearance as at the previous examination. There is marked redundancy of the mucosa throughout the entire stomach and the deformity of the duodenal cap is exactly the same. Diagnosis—Gastric polyposis."

Operation.—On June 3 1932, the abdomen was explored through an upper right rectus incision. The stomach wall was markedly hypertrophied. An active ulcer, about 1 cm in diameter was found on the anterior wall of the first portion of the duodenum. It was excised, and a posterior gastroenterostomy was done. The fixation of the duodenum made a prioroplasty difficult to execute and it was not at tempted. No other abnormality was found in the abdomen.

The patient a recovery was without incident and she has remained well.

OAST 2 -- M S., female, seven years old. This patient was seen in consultation with Dr Robert A Bler, who kindly furnished me data of which the following is an abstract:

Family History -- Father Flipino mother, Greek, patient born in France

Past History.—Early past history irrelevant except she has been somewhat under neurished and underdeveloped all her life. In January 1933 she was first seen and a diagnosis of juvenile pulmonary tuberculosis was made. She was seen at infrequent intervals until June 6 when x ray examination reported lungs exsentially clear

Present Illness.—July 21 1932 patient reported complaining of pain in the abdomen during the previous two days, following some indiscretion in dict. The physical examination was negative. In November 1932 patient's mother reported that the child had tarry stools in two successive days. Pain and fover were absent. The physical examination at this time was reported as follows

The patient is a small swarthy female seven years of age. Outside her under weight and marked anemic appearance the physical examination was essentially negative. The examination of the abdomen was carefully made but elicited no positive findings.

The Wassermann was reported negative a few days later

The stool showed blood in large quantities. The mother stated upon closer questioning that a tarry stool was noted about one year previously, but she falled to mention it until this time. The following day two more bloody stools were reported and patient was admitted to the Children's Hospital and a blood examination made at that time was reported as follows Hemoglobin 38 per cent (Newcomer), erythrocytes 2,500 000 leucocytes 8,200 lymphocytes, 90, polymorphonuclears, 70 lobulated, 64, band forms 4 young forms, 2.

Tuberculin test negative

Urine contained albumin upon the first examination but three days later albumin was absent

A few days after admission to the hospital the child complained of mild pain in the abdomen

The x ray examination of the gastrointestinal tract, made at this time, reads as "The esophagus is normal There is a constant deformity at the pyloris and at the base of the duodenal cap with approximately 10 per cent six hour Appearance is that of an ulcerative lesion at the pyloris. Appendix normal Colon normal throughout."

The patient was placed on a diet of the Sippy type and at last accounts was making excellent progress, without recurrence of blood in the stools Operation was not indicated, in our opinion

This presents almost a typical case of duodenal ulcer in a child, and if the bloody stools and vray examination could be eliminated from the history, the diagnosis would not be possible This emphasizes the importance of melena as a symptom and the necessity of vray examinations in suspected cases

# COMMENT

That a child may have a chronic peptic ulcei must be an accepted fact, and the few cases reported (excluding those attended with perforation) indicate that a better understanding of the symptomatology is necessary if the disease is to be recognized in a fair percentage of cases before a serious complication discloses the real nature of the There has not come to our notice any extended study of dyspepsia in childhood, having in mind the possibility of peptic ulcer, that included such examinations usually employed in the adult are convinced that such an investigation no doubt beset with many difficulties, would have its own reward in setting up a clinical concept of ulcer in children and permit a better classification of diseases that are obviously mislabelled

There is hardly a surgeon of wide experience who has not removed an appendix from a child in which the pathology found did not explain the symptoms The recovery of the patient is his chief source of comfort as he knows only too well that the diagnosis was missed That his consultants were equally wrong adds a little balm likely that some of these cases are peptic ulcers, as in one case herein 1 eported

Is it not possible that if the subject of dyspepsia in children were given the same intensive consideration bestowed on many other human ills, a group of symptoms would be found that makes the recognition of the disease possible in its early stages? At the present time no such group of symptoms, no x-ray studies, no pathological set-up is available, based on a large number of cases The need is apparent and no doubt will be met

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# THE SERUM ALBUMIN AND GLOBULIN OF NEWBORN, PREMATURE AND NORMAL INFANTS

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THE concentration of serum proteins has been studied for years However, most of the pediatric literature concerns determinations by physical methods (particularly by refractometry) which give large and uncertain errors. Recent work emphasizes the different functions of globulin and albumin. The physical methods for determining the albumin and globulin are even more erroneous than similar methods for estimating the total protein. Although the chemical methods occasionally give false results in the separation of the fractions of serum proteins a sufficiently true picture can be obtained in this way to warrant an examination of infants serum. This paper reports the total protein, albumin and globulin concentrations of newborn, nor mal infants from the fourth to the eighth month and premature in fants. In addition a few determinations in pathologic conditions are listed. The data form a standard for evaluating protein concentrations during the first year of life.

### LITERATURE

Mello Leitao<sup>1</sup> reviews the literature on serum proteins in infants estimated by refractometry. This work shows that the serum proteins are lower in young in fants than in adults and that the proteins increase gradually during the first eighteen mouths of life. Marriott<sup>2</sup> and others found the serum protein low in undernutrition and marsumus. Mello-Leitao obtained high values in congenital syphills.

Webb<sup>3</sup> using the colorimetric method of Wu which gives slightly high values for albumin found for young bables the following values total protein 6.04 per cent albumin 441 per cent and globulin 1.63 per cent. The rise in the total protein with age was shown to consist of an increase of proportionately more globulin than albumin Simple undernutrition gave essentially normal values. No striking change with infections was found except in bone tuberculosis esteomyclitis and infections accompanied by albuminuria. Infections of the bones were quite regularly accompanied by increase in globulin while albuminuria was accompanied by decrease in albumin and sometimes by an increase in globulin.

The association of the precipitin reaction with the globulin has led to examination of the effect of infections on this fraction of scrum protein. The occurrence of colon bacillus septiconia in calves which receive no colostrum was shown by Smith and Littles and Howes to be accompanied by a failure to obtain globulin.

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Inspection of the chait reveals that the total protein is widely scattered in each group so that there is considerable overlapping of single determinations of the various groups. The differences between the averages of the various groups ± the "probable error" of the differences are tabulated in Table I. Since a difference which is three times the "probable error" of the difference can only occur through chance sampling in about 5 per cent of the cases, such a difference

TABLE I

DIFFERENCE BETWEEN AVERAGE CONCENTRATION ± "PROBABLE ERROR" OF DIFFERENCE

	PER CENT PROTEIN	PER CENT ALBUNIN	PER CENT	<u>A</u> G
Normal-Newborn	$+0.76\pm0.11$	+ 0 55 ± 0 09	+ 0 23 ± 0 09	$-0.02 \pm 0.10$
Newborn—Premature	$+0.58\pm0.12$	$+0.15\pm0.08$	$+0.60\pm0.12$	$-0.73 \pm 0.09$
Normal-Premature	+134±010	$+0.70\pm0.09$	$+0.83 \pm 0.11$	$-0.75\pm0.09$

may be regarded as significant. This test of significance confirms the impression given by the chart that the concentration of the total protein is greater in the older normal infants than in the newborn and greater in the latter than in the premature. Although the average albumin of the premature infants is slightly lower than that of the newborns, this difference cannot be regarded as statistically signifi-

TABLE II
POSTMORTEM BLOODS IN FETURES

пт см	PER CENT PROTEIN	PER CENT ALBUMIN	PER CENT GLOBULIN	\\ \( \frac{1}{G} \)
650	4 02	2 63	1 39	20
780	5 19	4 04	1 15	3 5
850	3 50	1 54	1 96	0.8
1500	5 88	3 65	1.73	22
1400	3 58	2 51	1 07	23
1200	3 89	1 65	2 24	0.7
1500	4 10	3 13	0 97	3 2
1025	3 76	2 57	1 19	3 1
1900	3 32	2 31	101	23

cant However, the albumin of older normal infants is definitely higher than that of the other two groups. The globulin is also higher in the older normal infants than in the other two groups and higher in the newborns than in the prematures.

The use of the albumin-globulin ratio is not altogether satisfactory but is so generally employed that these values were computed. The latio depends on the accuracy of the determinations. Since globulin is determined by difference, any error in the albumin determination becomes greatly magnified in the albumin-globulin ratio. For this reason conclusions should only be drawn from changes in albumin or globulin concentration. Our data indicate that the proportion of globulin is reduced in premature infants.

Since the finding of low globulin in premature infants might depend on failure of globulin to develop till late in fetal life, several specimens of fetal blood were examined. In these cases for various reasons, labor occurred early but the fetus died late during labor or within one or two hours after birth. The blood was taken immediately after death. The results are given in Table II. We do not wish to draw conclusions concerning the concentration of albumin or globulin during fetal life from these figures, but merely point out that they do not indicate any decrease in the proportion of globulin in the serum of fairly small fetuses.

Since certain infections are known to raise the globulin, a study of the serums of babies with infection should reveal a failure of infants to react in the usual fashion. Table III gives results in various conditions. In the last four cases, the patients were prematurely born

TABLE III
SERUM PROTEINS IN IMPANTS WITH INFECTIONS

CABE	AGE B7ZG	BIRONDAID	DAYS ILL	PROT	ALB.	QLOB.	Ğ
1	330	Measles, Pneumonia	14	6.16	3.6_	2 52	14
2	210	Syphilis	210	7 08	4 08	3.00	14
8	250	Scurvy	601	6.89	3 48	2.91	1.2
4 5	150	Rickets, Eczema	901	674	8 41	3.33	1.0
σ	250	Otitia Media	90	7 75	3 78	8 97	10
6 7	330	Pertussis Pneumonia	80	6 62	4 10	2 62	16
7	65	Undernutrition	7	5.34	8 61	178	2.1
8	120	Pohomyclitis	10	5.84	3 05	1.29	18
9	210	Mental Deficiency	210	7 46	5 78	178	3.8
10	100	Malnutrition Diarrhea	1	5 74	4 14	1.60	2.6
11	180	Cerebral Palsy Unex plained Fever	28	6.22	3.90	2.27	17
12	270	Rickets Tetany Rhinorrhes	30	6.80	5 14	1 66	8.1
18	77	Microcephalus Otitis	14	6 41	4 68	1.78	2.6
14	180	Otitis Media Convulsion	18 14	691	4.81	2 60	17
15	180	Pneumonia	5	5.89	2.92	2 47	2.0
16	00	Syphilis	60	5.72	2.63	8 09	09
17	180	Otitis Media Diarrhea	7	6.82	4 18	2.14	20
18	200	Chronic Pneumonia	80	6 57	3.87	270	14
18	210	Ohronie Pneumonia	40	6.95	4 48	2.52	1.8
19	70	Pneumonia	70	6 26	4.88	1.93	2.2
19	90	Recovered	00	6.71	47	2,24	19
20	830	Otitis Media	10	674	4.19	2.55	16
21	360	Dermatitis 7	30	6.22	2.56	3 66	07
22	7	Neonatal Sepsis	1	6 05	2.99	8 06	1.8
23	120	Diarrhen, Otitis Media	10	7.10	5 48	1 62	3 4
24	80	Diarrhen Otitis Media	14	5 60	2.28	3.32	07
2.5	25	Diarrhea		4 14	2 77	1.37	2.0

We may conclude that single determinations almost certainly represent a deviation from normal when they differ from the average of their group more than two standard deviations. Since these babies are of the age of the group of normal infants, they should be compared

to the average of this group. Applying this criterion six albumins are low. Cases 3, 4, 8, 15, 16, and 21. Case 21 was a peculiar unclassifiable skin disease resembling Leiner's dermatitis exfoliativa, and was the only one manifesting edema. Undernutrition probably played a part in reducing the albumin in the cases of scurvy, eczema, pneumonia, and syphilis. Case 9 (mental deficiency) probably showed a high albumin because of an unsuspected dehydration. The globulin was high in Cases 2, 3, 4, 5, 6, 18, and 21. The most striking elevations are in the patients with syphilis and skin infections.

Since opportunity to study premature infants with infection who are not also dehydrated does not occur often, such cases are few in our series. Cases 24 and 25 suggest that premature infants are apt to develop low albumin with diarrhea and infection. Cases 20 and 24 demonstrate that premature infants can produce a high globulin content in their serums.

# DISCUSSION

The average values for adults (Peters and Van Slyke<sup>10</sup>) is for men, protein 700 per cent, albumin 444 per cent, globulin 258 per cent and A G ratio 172, for women, protein 702 per cent, albumin 435 per cent, globulin 268 per cent and A G ratio 162 Plass and Mathews,<sup>20</sup> Oard and Peters<sup>21</sup> and others have shown that a decrease in serum albumin occurs during pregnancy. Our data indicate that older normal babies have about the same albumin concentration as adult women, but slightly lower globulins. Thus the low proteins of infants is chiefly due to low globulins, though a reduction in albumin corresponding in magnitude to that occurring in pregnant women, is found in newborn infants. In this respect premature infants are like newborn infants, except that their globulin tends to be even lower

The data on the premature infants showed no relation between the various protein constituents and the age, the birth weight, birth length and the weight at time of examination. The low albumin may be characteristic of small babies since none of these infants weighed over 2900 grams when the blood samples were taken. Six samples taken during the first thirteen days of life did not differ sig inficantly from the group as a whole. The ages range from six to ninety days, but most of the examinations occurred between the twentieth and fortieth day after birth

The work of Achard, Bariéty, and Codounts demonstrates that infants are born with about the same concentration of albumin as their mothers, but with definitely lower globulins. This fact suggests that albumin may diffuse across the placenta but apparently globulin behaves somewhat differently. The production of albumin is interfered with in severe undernutrition (Bruckman, D'Esopo and Peters,<sup>22</sup> Frisch, Mendel and Peters,<sup>23</sup> Weech and Ling<sup>24</sup> and others). Our data indicate that albumin concentration is more constant than globulin

concentration. After depletion of serum proteins by plasmapheresis, globulin is regenerated more rapidly than albumin 14 Globulin appar ently increases greatly beyond its usual concentration in response to tissue injury 10 and certain infections 2. Since babies during the first few months of life have suffered from few infections, these observa tions suggest that infants may have low concentrations of globulin largely due to absence of the stimuli which lead to globulin production ın adıılta

#### SUMMARY

The serum concentration of total protein, albumin and globulin was determined in 20 newborn infants, 14 normal infants, aged about five months, and 26 premature infants. Similar studies in full term and premature infants suffering from various diseases were made

The total protein is decreased in all infants, the decrease being due chiefly to low globulin. The diminution in globulin is greatest in premature infants

Postmortem serum of small fetuses shows essentially the same al bumin globulin ratio as that of full term infants

Both premature and normal infants may show an increase in globulin during infection

It is suggested that the low globulin in infants may indicate the lack of the usual stimuli that give rise to globulin production in adults

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# MANAGEMENT BY MECHANICAL RESPIRATOR OF POSTDIPHTHERITIC RESPIRATORY PARALYSIS

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THE clinical similarity of respiratory failure in late diphtheria and in certain forms of poliomyelitis is apparent to physicians familiar with the two diseases. Wilson¹ has emphasized that poliomyelitis can pievent efficient respiration through direct paralysis of the primary respiratory muscles, through interference with respiration in patients with pharyngeal paralysis in whom inspiration is continually interrupted by unswallowed secretions collecting around the glottis, and finally through a disturbance of the nerve centers in the medulla controlling respiration. Respiratory difficulty in any patient ill with poliomyelitis may be due to a single one of these factors or to a combination of two or more.

The striking difference between respiratory difficulty in poliomyelitis and in late diphtheria is that in infantile paralysis the cause is commonly of central origin, while in diphtheria the difficulty is chiefly concerned with paralysis of the diaphragm and of the intercostal muscles. In both conditions the factor of accumulated secretions following paralysis of the muscles of the pharynx is often important. The careful observations of Wilson have demonstrated that in poliomyelitis the response to management with the Drinker<sup>2</sup> respirator is much more favorable when the lesion is related to the cervical and dorsal coid, with resultant paralysis of the intercostal muscles and of the diaphragm, than when the involvement is primarily bulbar. Our own experience has been the same, and logically led to consideration of this method in the management of late respiratory paralysis in diphtheria

Since 1927, 5057 cases of diphtheria have been admitted to the wards of the Herman Kiefer Hospital, Detroit—The number of deaths was 632, of which an appreciable number, eighty-seven, were due to the toxic effects of the infection and occurred within the first few days—Circulatory failure was by far the commonest cause of death, being responsible for no less than 415 fatalities—Among patients with the laryngeal form of diphtheria the commonest contributing cause of death was pneumonia, ninety-six cases, with suffocation from obstruction essentially uncommon Septicemia, generalized suppurative peritonitis, nephritis, empyema thoracis and activated pulmonary tuberculosis were rare causes—Fatality in thirteen instances was due to respiratory insufficiency after paralysis,

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or about 2 per cent of all deaths. The condition is not frequent but when it does occur is of serious moment, in that of twenty-one patients with diaphragmatic and intercostal paralysis thirteen died, a case fatality of 619 per cent.

Paralysis of respiratory function in diphtheria is as a rule a late development. The condition is almost completely limited to patients with an original massive infection of the throat, where the membrane in volves not only the fauces but extends into the masopharyngeal vault and generally involves the palate and the uvula as well. The first paralysis to develop is ordinarily related to inhibition of function of the palate, and would seem to depend largely upon local absorption of toxins. It usually appears on the eighth to fourteenth day after onset. The paralysis next most commonly observed involves the muscles of the eye. At about this same time, the third week, a paralysis of the muscles of the larynx and of the pharynx may occur. By the fourth week the muscles of the extremities are likely to be involved and not uncommonly sensory disturbances are present, indicated by numbness, prickling and hyperesthesia of the extremities. Respiratory paralysis rarely develops other than in the wake of such a progression of paralyses.

In this group of patients the earliest onset of respiratory paralysis was on the twenty-seventh day the latest on the fifty sixth. The course of events in overwhelming faucial diphtheria is a severe toxemia lasting four to five days, followed almost invariably by severe circulatory disturbance on the eighth to sixteenth days. In those surviving this hazard paralysis of the muscles of respiration may be anticipated about the sixth week. The time of this reaction is so constant that trouble is looked for at about the thirty fifth day in the hospital which corresponds to about the fortieth day of the disease. Our experience in the onset of respiratory paralysis is illustrated in Table I

Since paralysis of respiratory function occurs only in late convalescence all deaths from diphtheria have been reviewed in regard to the day of the disease on which they occurred. Of the 632, only twenty nine were after the twenty first day. Of these thirteen were due to paralysis of the muscles of respiration ten to circulatory failure and six were attributed to bronchopicumonia. Postdiphtheritic paralysis is thus the most common cause of death during convalescence.

TABLE I

DAY OF ONSET OF POSTDIPHTHERITO RESPIRATORY PARALYSIS

DAY OF ONSET	Q78EE
21 - 2	1
28 - 34	8
<b>35 - 41</b>	11
42 - 48	5
49 - 55	0
56 - 62	1

Dimker in 1929 reported a mechanical apparatus for maintaining prolonged artificial respiration and gave a description of a fatal case of poliomyelitis treated by the method Later he presented an analysis of additional cases, suggested the use of the apparatus in the orthopedic treatment of intercostal paralysis, and reported on its use in seventeen cases of gas poisoning, eight of alcoholic coma, five of drug poisoning, and one of drowning Jackson has described the development of mechanical methods for prolonged respiration. Murphy<sup>5</sup> and others reported a modification of the original Drinker apparatus designed for small children and infants, with an appliance for the administration of oxygen and carbon dioxide in the treatment of asphysia of the new-Murphy, with C K Drinker and Philip Drinker,6 emphasized that respiratory paralysis in the presence of an exudative process in the lungs is likely to make but little progress when managed by the Reports on the method in poliomyclitis complete the literature 7 To these indications may now be added another, the application of the method to postdiphtheritic respiratory paralysis

Case 1 — Elizabeth K, aged eight years, became ill on December 1, 1931, with sore throat, fever, and headache. The next day the glands of the neck were swollen, she vomited twice and complained of constipation. A well marked discharge from both nasal passages was present on the third day and the swelling of the neck was evaggerated. She was not seen by a physician until late on the fourth day. He administered 10,000 units of antitoxin and sent the child to the hospital.

The temperature was then 1024° F, the pulse rate was 120 and the respiratory General physical examination indicated a child critically ill a mucopurulent discharge from both nares The neek was so swollen, because of enlargement of the cervical lymph nodes and the adjacent tissues, as to produce a rounded effect almost obliterating all markings and suggesting the possibility of The tongue was markedly coated The tonsils were so enlarged and swollen that they essentially met in the midline of the throat. A thick diphtheritie membrane covered the entire surfaces of both tonsils, all visible portions of the pharyn, the uvula and the soft palate Both lung fields were clear borders were within normal limits No murmurs were heard. The cardiac sounds were well preserved and the rhythm regular The child was poorly nourished and Sixty thousand units of diphtheria antitoxin were administered on the eve ning that the child came to the hospital, and an additional 40,000 units the follow ing morning On the sixth day of illness, the patient was clinically much worse, and the blood pressure was at the extremely low level of 72/48 The cardiac tones were softer and the heart rate more rapid

On the fourteenth day the blood pressure dropped sharply to a level which long experience has shown to be compatible usually with no other than a fatal prognosis the systolic pressure being 54 and the diastolic indeterminate. A marked gallop rhythm was present. For the next several days the child was listless, took nourish ment and fluids poorly and barely seemed to live from day to day. Palatal paralysis was first noted on the twenty first day and shortly thereafter paralysis of the muscles of the pharyny, accompanied by the collection of much mucus in the throat because of inability to swallow. Repeated aspiration was performed with a mechanical suction apparatus. On the twenty fourth day the patient complained of blurring of vision, and within the next two or three days, of general hyperesthesia, par ticularly numbress and tingling of the extremities. By the thirty seventh day the

paralysis of the thront had become so extensive as to necessitate feeding by masal entheter. The circulatory condition was somewhat improved. Throughout the forty second day the patient was fairly quiet but in the early evening became restless and eyanotic from insufficient exygenation. At 10 30 PM the respiratory effort was of such degree that the patient could not be restrained. She continually tossed about and attempted to sit up. Paralysis of the interestal muscles, which had been first noted three days previously was at this time so extreme that breathing was almost cutirely abdominal. It was felt that exitus was imminent unless aid to respiration could be accomplished. During the course of transfer from her room to the mechanical respirator the child a struggle for air ceased and there was a gurgling shallow tyre of breathing indicative of complete exhaustion.

The child evidenced a remarkable change shortly after being placed in the respirator. Within an hour all restlessness had disappeared and she slept comfortably the remainder of the night. The color of the lips and nail beds im proved. During the early hours of treatment a pressure of 18 to 20 mm was used but the next morning this was reduced to 8 mm with equally good effect. The following day the patient slept a goodly portion of the day although the machine was continuously in motion. Mucus continued to collect in the throat and was a troublesome factor which demanded repeated use of the aspirating apparatus. The following three or four days were uneventful. On the fifth day the child was out of the respirator twice for periods of six and ten minutes during which time respiration was fairly regular but rapid and somewhat shallow with movements of the chest exaggerated. After seven days the respirator was no longer required except for periods of exercise. Active respiration was much improved although the accumulation of mucus in the throat continued a matter of concern. Con valescence was progressive so that by the seventy eighth day she was able to be up for the first time and on the eighty fourth day was discharged from the hospital recovered.

Cast 2—John W aged eighteen years became ill on April 3 1082 with sore throat and fever of undetermined degree. The next day he complained of chillness, of aldominal pain and vonited several times. Headache became a pronounced symptom. Swelling of the glands of the neck was first noticed on April 4. During the next two days his illness progressively became of greater moment although he was not seen by a physician until April 7 the fifth day of his illness.

The patient was admitted to the hospital in a critical clinical condition. The fover was 101 6 F., the pulse rate was 88 and the respiratory rate 20 The lips and nail heds were deeply cyanosed. The patient was rational, cooperative but markedly taxle. The swelling of the neck was not limited to the lymph nodes but involved the tissues about the glands, to give a periadentitis and edema of extreme degree. A gray white membrane covered both tousils extended upward to involve the nasopharynx and forward to completely cover the urula, the entire soft palate and even part of the hard palate. The distribution of diphtheritie membrane and the severity of the general reaction were about as severe as may be seen in malignant diphtheria. The heart rate was slow but regular. The heart tones were ill defined and muscular. No murmurs were heard.

Antitoxin in the amount of 80 000 units was administered immediately with an additional 40 000 units the following day. The patient s condition was extremely precarious during the early days in the hospital, subsequently slowly improved and the mucous membranes of the pharyax were first entirely free from membrane on the eighth hospital day. The blood pressure which at the time of admission was 100 mm. Hg systolic and "0 diastolic dropped at this time to 82/50 and the heart tones were only of fair quality. On the fifteenth day the patient was very pale and the pulse rate had dropped to 52. There was every clinical evidence of myocarditis

with impending circulatory failure of diphtheria, and complaints of nausca and epigastric pain. The following day a gallop rhythm was well defined. The blood pressure was 75/40. The liver was tender and palpable. Palatal paralysis was noted. On the eighteenth day the quality of the heart sounds was somewhat im proved, also the rhythm, and the blood pressure was slightly higher. Dating from that time there was well marked improvement, so that by the twenty fifth day the pulse rate was 80 and the blood pressure was 96/66. For the first time, however, he complained of difficulty in swallowing and this was accompanied by an irritative cough.

No distinct advance occurred in the paralysis of the muscles of the pharynx until the fortieth day, when the voice developed a marked nasal quality and the paralysis became so well defined that he had emesis of food through the mouth and nose. The quality of the pulse was not as satisfactory. He spent a restless night. Be cause of repeated emesis, nasal feeding was instituted. On the forty first day the respirations were irregular and somewhat shallow, although the pulse was stronger. The patient slept a great deal. He complained of blurred vision. In the course of the early afternoon respiratory effort became pronounced and at 4.45 he was placed in the Drinker respirator, cyanosis being then very definite and the respirations so labored as to be alarming. The pulse rate was 140, and the temperature had increased to 101° F. The paralysis of respiration was distinctly of the intercostal muscles, in that although the rate of respiration was rapid there was little movement of the chest. It was believed that bronchopneumonia was also present.

The pressure of the machine was maintained at 18 to 22 mm and the rate at 16 and later 32. At no time could the patient accommodate respiratory effort to the rhythm of the machine. He progressively became worse and death occurred at 10.05 PM, essentially five hours later.

# DISCUSSION

The clinical similarity between postdiphtheritic respiratory paralysis and that form of poliomyelitic paralysis reacting most favorably to management with the Drinker respirator indicated the probable value of the method in diphtheria. Our experience would suggest another worth-while use of the method in the field of communicable disease

In criticism of the conduct of these two cases, we feel that the observation of Wilson applies pertinently here as in poliomyelitis, in that both patients might well have been given earlier advantage of the method. The patient who recovered was placed in the machine within minutes of an expected exitus, and the one whose illness terminated fatally might well have received material benefit by its use at least three days earlier. Our experience with this method in poliomyelitis had been discouraging, to such an extent that we hesitated to make use of it in diphtheria unless no other measure was possible. With the earlier types of apparatus it was difficult to provide ordinary symptomatic and hygienic care. This is not a criticism of the more recent models of the respirator.

If artificial respiration by this method is started at the first sign of difficulty it is believed that a greater proportion of recoveries will be noted among patients with postdiphtheritic paralysis than with any other of the conditions which may be treated by this method

#### CONCLUSIONS

The use of the Drinker apparatus for long-continued artificial respira tion forms a worth while addition to present methods of management in postdiphtheritic respiratory paralysis. Two case reports describe one recovery and one death. The early use of the method should conduce to fewer deaths from this uncommon but serious complication of diph thems

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spinal roots and the cauda equina. Plexiforme neuromas are quite similar to the multiple neuromas, the main difference lying in the fact that only a small group of nerves is affected, the lesions being more encumscribed. At times, the involvement may be so great that considerable enlargement of the extremities occurs, the condition then being known as elephantiasis neuromatosa (pachydermatocele). Pigmented nevi are commonly present as associated lesions of the skin, and occasionally "port-wine" nevi and the so-called anemic nevi of Vorner. It should be stated that according to Antoni, the tumors of you Recklinghausen's neurofibromatosis are made up characteristically either of apolar tissue (type B) showing no palisading of nuclei or polarization of cells, or, at times, of tissue of the A type, the true perineural fibroblastomas which are of neoplastic nature and composed of fibroblasts displaying both palisading of nuclei and polarization of cells

In cases of neurofibromatosis, the pigmented eruption of the body, or "café au lait" spots, has always attracted attention. It is usually found scattered negularly over the body Its relation to the problem of the origin and formation of skin pigmentation is of particular interest Blocks believes that there are two types of skin pigment cells, the melanoblasts, comprising those cells which are capable of forming pigment, and the melanophores or chromatophores, consisting of those cells which cannot elaborate their own pigment but which obtain it from other sources The human skin contains pigment in its ectodermal and mesodermal parts The ectodermal pigment cells of the skin. as well as of the mucous membranes, are melanoblasts of ectodermal origin and are found in the epidermis, especially in the basal cells, the hair matrix and in the cells of pigmented nevi. The mesodermal part of the skin, the corium, contains two different kinds of pigment cells The one type, melanophores, which have phagocytized pigment, is found in the papillae and in the deeper layers, whereas the other type, mesodermal melanoblasts which have elaborated their own pigment, is found in the cutis Moehligo states that both the posterior portion of the pituitary gland and the suprarenal cortex are concerned with pigment formation, the latter reflecting or mirroring the state of the former Posterior pituitary lobe extract is a melanophore stimulant and affects particularly mesodermal tissue The pigmentary changes occurring in von Recklinghausen's neurofibromatosis have been attributed to a disordered state of the adrenal glands Many cases have been reported in the literature, such as those by Levin10 and by Tucker, 11 which seem to show a relationship between certain endocrine The latter author states that dysfunctions and neurofibromatosis from the pituitary standpoint the characteristics are chiefly acromegalic in type, whereas the suprarenal manifestations are pigmentary disturbances, lowered blood pressure, and hypotrichosis

The true character of the osseous lesions in neurofibromatosis was first described by Brooks and Lehman<sup>12</sup> who found the following types of bone changes which were considered characteristic of the disease scolosis, abnormalities of growth, irregularity of the shafts of the long bones, and subperiosteal bone cysts. The irregularity of the shafts of the long bones varied from slight change in outline of the perioateal and cortical structures to large tumors projecting from the surface of the bone or embedded as cyst like cavities in the structure of the bone Microscopically, the central portion of the tumor was found to consist of tissue similar to that of the cutaneous lesions, as well as of some newly forming bone. The investigators were of the opinion that the changes were induced by the development of neurofibromas along the nerve filaments in the periosteum, thereby setting up a certain amount of reaction and causing bone destruction and regeneration has attempted to classify the various osseous lesions, defining them as manifestations of the complicated disorder of neurofibromatosis and comparing them to its skin and visceral expressions Recently, Weber,14 in an article dealing with periosteal neurofibromatosis, also expressed the opinion that in certain cases of von Recklinghausen's disease bony thickenings occur which are due to involvement of the periosteum

It should be borne in mind, however, that von Recklinghausen's neurofibromatosis is not seen always in its complete clinical form. As Goodhart<sup>15</sup> has stated. 'Aside from typical forms of neurofibromatosis, there are also incomplete or abortive forms in which only one of the cardinal symptoms is present, either pigmentation or fibroma which may be not infrequently combined with mental defects or skeletal anomalies.' Many years ago, Weber. called attention to the fact that cases occur in which pigmentation of the skin is manifest long before the appearance of neurofibromas of the nerve trunks or tumors of the skin, citing many case records to bear out his contention

The following case reports illustrate the above statements

Cass 1.—J E male white was born at full term on October 8 1922. The second stage of labor was prolonged and was terminated by the application of forceps. Marked eechymoses and swelling were present about the infant's eyea. Respiration was spontaneous there were no convulsions. The birth weight was 104 pounds (4 76 kg). The mother a primipara, was thirty one years of age and had been married eleven years before giving birth to this boy her only child. Through out pregnancy she had maintained good health. There were no previous miscar riages. The father thirty-eight years of age was normal physically. The family history was essentially negative

The infant was fed artificially and manifested an excellent rate of growth, weighing 25 pounds (11.4 kg) at the end of the first year of life. Development was also normal. Of importance in the light of future developments, is the fact that shortly after the birth of the infant, the mother noticed a few scattered areas of brown ish pigmentation on his body. However little attention was paid to the cruption at this time. It should be stated here that the pigmentation became more evident sub-

sequently, new areas appearing on the trunk, face, and extremities, each lesion growing in size and deepening in hue. Aside from an attack of whooping cough when he was three vears of age, and a retropharyngeal abscess at three and one-half years of age, the boy enjoyed apparent good health up to about five and one half years.

At this time, he was seized suddenly at night by an attack of projectile vomiting which was followed shortly by a series of convulsions lasting about twelve hours. The temperature was high. He was taken to one of the city hospitals where he was observed for a period of three weeks, no definite diagnosis being made. Following this primary acute attack, the boy became subject to the frequent occurrence of convulsions, both minor and major in severity, some being of but brief duration whereas others lasted from ten to fifteen minutes. For the most part they took place at night while the boy was asleep. They were preceded invariably by sharp piercing cries, pallor and comosis and were followed by clonic contractions of the entire body and a period of unconsciousness. At no time was there frothing at the mouth, biting of the tongue, or loss of sphineteric control. Vomiting did not occur always. Other episodes consisted merely of a trembling of the entire body and momentary loss of consciousness. The attacks occurred irregularly, sometimes taking place daily, whereas at other times an interval of a few weeks clapsed between attacks.

At six and one half years of age, the boy entered public school, where it was noticed that he had poor eyesight. He was placed, therefore, in the sight conservation class. He was then referred to the Neurologic Institute for examination. It was noted by roentgenograms that the skull showed a tendency toward early union of the sagittal suture but that this had not vet produced demonstrable change in the outline of the skull. The sella turcica appeared to be normal and secondary dentition was progressing favorably. The blood gave a negative reaction both to the Wassermann and Kahn precipitation tests. The von Pirquet test was negative and the basal metabolism was recorded as being minus 3. Of interest is the fact that psychometric tests were performed at this time, with an intelligence quotient of 102 on the Terman scale.

As far as the general behavior of the box was concerned, he was well mannered and obedient, amenable to discipline, and never assaultive. His personal habits were good. In school, he associated well with his classmates and showed slow but definite progress in class work, despite frequent periods of absence. Meanwhile, it was noticed by the mother that the pigmented areas on the face and body of the boy, were increasing in number and in size and were becoming deeper tan in color. It was also observed that the was developing a hard tumor on the right side of the nose, directly beneath the inner portion of the right eye. The boy was then referred for admission to the Beth Israel Hospital

He was now eight verrs of age, weighed 70 pounds (318 kg) and was 55 inches (139 7 cm.) in height. His head measured 21% inches (55 cm.) in circumference, his chest  $26\frac{1}{2}$  inches (65 5 cm ), and his abdomen  $25\frac{1}{2}$  inches (64 8 cm ). He was The musculature was flabby and the fairly well developed and of fair nutrition posture poor He was restless and mattentive. He appeared to be dazed and dis oriented, his responses showed a markedly delayed reaction time. Over the entire trunk, face, and extremities, but mainly over the covered parts of the skin, there was seen a generalized, haphazardly arranged, irregularly oval shaped, pigmented macular eruption, the lesions varying in size from that of a pinhead to 4 or 5 centimeters in longest diameter (Fig 1) Their color ranged from pale ian to light brown. They were equally numerous both on the dorsal and ventral aspects of the trunk and extremities Directly above and to the outer side of the right nipple The skin, which was moist and coarse, there was seen a deeply pigmented nevus had a peculiar pale yellowish hue. There was a normal growth of lanugo hair. At this time, no tumor masses were palpable in or beneath the skin

The head was long and narrow and appeared to be too large for the rest of the body The upper and lower jaws were prominent and the upper middle incisor teeth protruded forward markedly. The general features were gross and coarse and suggested a disturbance of the pituitary gland. It should be noted in this con nection, that the fingers of the hands were long broad and spatulate at the tips The scalp was covered by coarse straight medium brown hair the cycbrows and eyelashes were normal. The nose was broad both at the base and at the bridge To the right side there was a bony hard swelling apparently intimately connected with the masal bone. The overlying skin was freely movable. The pulpebral fissures were equal there was about a 20 degree convergent strabismus of the left eve

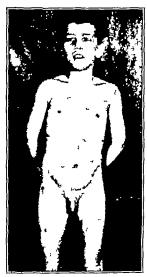


Fig 1—Showing the irregularly cattered oval-shaped, pigmented cruption of the body. Note also the bon, tumor on the right side of the nose and the internal strabismus of the left eye.

The right pupil was greater than the left both reacted normally to light and accommodation. The aculty of vision was \_0/100 for the right eye and 0/200 for the left there was a bilateral myopic astigmatism. The fundi showed a primary optic atrophy Attempts to catimate the fields of vision either by confrontation or by perimetry were unsuccessful. The ears were normal. The lips were thickened the vermillon borders being fairly well defined. The upper inclsor teeth were larger than normal and protruded forward markedly. The enamel of the permanent teeth was The decidnous teeth showed well advanced caries. All the teeth were poorly spaced the occlusion was had. The mucous membranes of the month were of good color The tongue throat, and pharvnx were normal There was no lymphadenop athy

The thorax was symmetrical and the nipples were normal. The lungs and heart were normal. The abdomen was soft, no organs or masses were palpable. The genitals were normal in appearance and the testicles fully descended. With the exception of the broad, flat hands, as has been mentioned before, the extremities were normal, as were the nails of the fingers and toes. Both the superficial and deep reflexes were equal and active, no pathologic reflexes were elected. The skin was hyperesthetic over all areas.

Laboratory procedures showed that the urine and the blood were normal. The latter gave a negative reaction to the Wassermann test. Glucose tolerance tests were performed, but gave no conclusive information. The spinal fluid showed negative reactions to both the Wassermann and colloidal gold tests. A basal metabolism was attempted under conditions not truly basal and showed a rate of plus 18



Fig 2—Atrophy of the bones of the hands involving the epiphyses and diaphyses but being more marked at the epiphyseal ends. Note beginning cyst formation in head of first metacarpal bone of left hand.

Roentgenography of the skull revealed that the cranial cavity was somewhat large, particularly in the postauricular portion. The bones of the cranium were of normal thickness, there were no areas of bone destruction or sclerosis and the sutures were not separated. The sella turcica was normal and the air sinuses were well developed. In the right infraorbital region, in the neighborhood of the superior maxilla, there was seen a bony mass which showed normal bone markings and which appeared to be a part of the ethmoidal cells. This mass was evidently that seen externally to the right side of the boy's nose. Encephalography failed to show any definite pathologic condition of the brain. Roentgenograms of the bones of the hands revealed atrophic changes involving the carpal and metacarpal bones, as well as those of the phalanges (Fig. 2.) The atrophy was very distinctive and involved the epiphyses and the diaphyses, but was most marked at the epiphyseal ends. In the head of the first metacarpal bone of the left hand, there was seen coalescence of several lamellae

which abowed changes resembling beginning cyst formation. Similar changes were found to be present in the bones of the metatarsal phalanges, as well as in the bones of the shoulder and hip joints. Films of the chest revealed nothing unusual

After a prolonged period of observation in the hospital, during which time the boy had but one mild attack of convulsions, he was discharged Since then for the past year, the convulsive seizures have occurred frequently, being both of minor and major severity Whereas previously they took place about once a week, of late they have happened almost daily Throughout all this time, his general behavior has been fair However, he has been showing signs of progressive mental and physical deterioration. Mentally, he is unable to grasp new situations easily, his reaction time has increased considerably, and he appears daxed and inattentive He is unable to concentrate on even the simplest problem and his answers to questions are ir relevant. He seems also to have reached the limit of his learning capacity

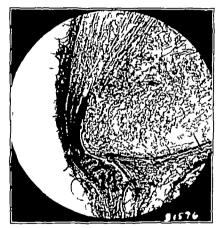


Fig. 3 -- Photomicrograph of section of subcutaneous nodule showing nerve trunk and tumor

Physically he has shown a slow but stendy loss in weight. Transient pathologic reflexes appear from time to time. He walks shakily swaying from side to side and shows a general lack of motor coordination.

At a recent follow up examination it was noted that several small subcutaneous nodules had developed bilaterally along the course of the superficial branches of the ulnar nerves. In addition a few had appeared in the occlipital areas of the scalp. The boy was then readmitted to the hospital and a blopsy was performed, two of the subcutaneous tumor masses being removed. Grossly the specimens consisted of spindle-shaped swellings having smooth shiny gray surfaces and were firm and elastic in texture. The microscopic report confirmed the clinical diagnosis of von Recklinghausen's neurofibromatoris. The spindle-shaped swellings consist of a highly edematous network of fibers. The fibers are coarser in the center thinner at the periphery. The officers are continuous with fibers from the nerve which are stretched over the node. How far these fibers belong to the nerve proper how far to the endoneurium cannot be said with cer-

tainty The same doubtful behavior is evidenced in the van Gieson stain, where the thicker fibers become intensely red, while the thinner ones, which are continuous with them, are definitely vellow. There is a very fine network of yellow fibers through which nuclei are spread in irregular fashion. Most of the nuclei are ovoid or spindle shaped. Occasionally, larger, faintly staining plasmatic bodies are seen around the nucleus. In the nonthickened portions of the nerve at the end of the specimen, the endoneurium appears much thickened. On the cross section, how ever, the medullary sheath and axis cylinders appear normal, as far as can be judged in this preparation." (Fig. 3.)

Comment—In recapitulation, Case 1 is one of neurofibromatosis in a young boy, nine years of age, showing clearly the systemic nature of the disorder. The boy presented pigmented lesions of the skin, subcutaneous peripheral nodules, and definite bony changes. In addition, there were signs of involvement of the central nervous system, as was manifested by epilepsy, signs of progressive mental deterioration, and changes in the optic nerve discs, as well as by aeromegaloid features. Of interest is the fact that the "cafe au lait" spots were noted should after the birth of the child. The onset of convulsions came about five years later. Bony changes were noted when the boy was about eight years of age whereas the peripheral neuromas appeared only recently.

CASE 2—D W a whate girl, four years of age, was admitted to the Beth Israel Hospital on December 15, 1931, because of a marked swelling of four days' duration on the back of the left shoulder. The complete history, however, antedated considerably this present period of illness, for, during the previous year and up to about four weeks prior to admission to the hospital, the child had been subject to the irregular appearance of small tumors over the scalp and forehead. They were neither painful nor tender, lasted a short time, and disappeared of their own accord. They caused no impairment of the child's physical development or any change in her general behavior. At no time was there fever or other constitutional symptoms. An interval of about one month lapsed following the subsidence of the last swelling, when the mother noticed the presence of a new, rapidly growing mass over the posterior aspect of the girl's left shoulder. The swelling was much larger than any of those which had occurred previously, but again, there were no general symptoms, whereas locally there resulted only slight limitation of motion of the left arm and some stiffness of the neck

As far as the child's developmental history is concerned, it was apparently normal in all respects. She was born at full term and weighed 514 pounds (2.38 kg) at birth. The delivery was normal, respirations were spontaneous, and there were no convulsions. The child was breast fed for a period of five months and then was given cow's milk and the usual mixed diet. The trend of motor development proceeded normally. At four months, the child was able to support its head. She sat up erect at five months, crept at seven months, stood up supported at eight months, walked freely at fourteen months, and spoke single words at twelve months of age. The first tooth erupted at about six months. Aside from a bilateral suppurative cervical adentits at two years of age, the child had always enjoyed good health.

The family history was essentially negative. The mother, thirty one years of age, the father, forty years of age, and their only other child, a boy of twelve years, were all normal physically. There was no history of familial or hereditary diseases either in the maternal or paternal branches of the family

Physical examination showed a quiet, mild mannered, obedient little girl who was in no apparent pain or distress. The body temperature was 90.4 F., the pulse rate was 110, and respirations 28 per minute. She was well nourished and had good musculature and color. Her weight was 30½ (17.7 kg) and her height 40 inches (101.6 cm.). The circumference of the head was 18¾ inches (47.6 cm.) and that of the chest 22%, inches (57.8 cm.). Her neck and head were held in a protective posture and there was some limitation of motion of the former to the left. The left arm was favored and could neither be raised above the level of the shoulder nor rotated without resistance on the child's part. The pectoral and scapular groups of muscles on the left side seemed peculiarly spassic to palpation. Over the left shoulder was seen a large diffuse swelling which extended anterforly outward and forward from the base of the neck to the supraclavicular area, and posteriorly backward and downward to a point below the tip of the scapula. Laterally it ex





Fig. 4—A Photograph taken on admission to hospital, showing the diffuse swelling of the left side of the back and of the left side of the neck. B Showing the marked swelling of the left pectoral region occurring three months later

tended from the spinal column to the posterior axillary line. (Fig. 4.4 and B.) The mass was warm firm brawny and slightly tender. Its edges were poorly defined and merged with the adjacent tissues. It was intinuately attached to the under lying structures and to the overlying integument which was reddened tense and somewhat glossy. The superficial voins showed prominently. Comparative skin temperature determinations revealed little thermal difference between the swollen area and a symmetrical area on the opposite side. Directly below the large mass, a smaller, but similar swelling was also present. There was some brawny edema of the supra puble region. Elsewhere the skin was smooth, moist, and showed the usual growth of lanuge hair. There was no regional or general lymphadenopathy.

The head was symmetrical and the scalp as well as the eyebrows and cyclashes showed a good growth of soft, smooth, medium brown hair. The palpebral fissures

and the pupils were equal, the latter reacting promptly to light and accommodation. The eyegrounds were normal. The nose, mouth, throat, and ears showed nothing abnormal. All of the deciduous teeth had erupted, they were well formed, had good enamel, and showed no evidence of caries. As has been stated, the neck showed marked fullness on the left side. The trachea was in the midline, there were no abnormal pulsations. The heart, lungs, and abdomen were normal. The liver and spleen were not enlarged. The extremities were normal with the exception of limitation of motion of the left arm. The nails of the fingers and toes showed nothing unusual. Superficial and deep reflexes were equal and active, there were no abnormal reflexes.

The urine, blood counts, differential smears, and chemistry of the blood were normal. The Wassermann reaction of the blood and the von Pirquet test were negative. Roentgenograms of the cliest, cervical and thoracic vertebrae, and of the left shoulder girdle revealed nothing of importance. Films of the skull showed changes suggesting an internal hydrocephalus. Bearing in mind the possibility that the swellings might have been allergic in origin, various protein sensitivity tests were done, but they gave no definite information.

During the early part of the child's stay in the hospital, the mass on the left side of the back, fluctuated in size, sometimes appearing smaller and being softer to touch, whereas at other times it was considerably larger and firmer of motion of the left arm became more marked, as did the spacticity of the under lying groups of muscles It was thought that microscopic examination of the tissue which formed the mass, would be of value in the diagnosis of the case Accordingly a biopsy was done, the smaller swelling being excised under local anesthesia gross pathologic examination showed a piece of skin having a thick, glassy sub cutaneous layer which measured about 14 centimeters in depth the upper layers of the skin were normal, there was no trace of edema was normal, as were the upper layers of subcutaneous fat. In the deeper tissues, however, there was seen a fibroma containing some nerve fibers at its periphery (Fig 5) According to the report of the pathologist "The tumor obviously be longs more to the fibromatous type of Recklinghausen's disease Nerves are seen at its periphery They are well separated from the surrounding tumor tissue low magnification, the interlacing of fibers immediately evokes the idea of neuro fibroma. Throughout the tumor, thick, obviously fibrous, bands are seen stained intensely with the acid fuchsin. The remainder of the tumor consists of a fine reticulum which assumes an orange hue in the van Gieson stain. At many points it has a similarity with nervous tissue, but there is no definite proof elongated, fairly light staining nuclei show fibrillary prolongations at many points. Whether or not the reticulum has been formed by these cells cannot be stated There are some groups of larger cells which are not characteristic of any definite No palisade arrangement of nuclei is seen histologic structure situated way below the cutis, therefore nothing can be said about its relation to the sweat glands Diagnosis Neurofibromatous type of von Recklinghausen's disease "

After a period of observation, the child was discharged from the hospital. The swelling had subsided considerably, but the area remained indurated. The subsequent clinical course is of interest, in so far as new tumor masses appeared from time to time in different regions of the child's body. These swellings grew slowly, were similar in appearance and, after reaching their height of development, subsided gradually but never disappeared entirely. About one month following her discharge, the girl was seen in the follow up clinic. Some swelling was still present on the left side of the back. There also seemed to be beginning involvement of the entire left pectoral area. The subcutaneous tissue was brawny to palpation. The left arm could not be raised voluntarily above the level of the shoulder, the under lying muscles were spastic. The right side of the back also showed evidence of in

volvement, for just to the right of the spinal column, at the level of the lower theracic vertebrae, a tumor measuring about 4 by 6 centimeters was visible. At the next examination, a month later a new swelling was seen on the posterior aspect of the right side of the neck causing considerable limitation of motion of the head. Shortly after a large mass developed over the left pectoral region. This swelling was again firm, warm, somewhat tender, and indefinitely demarcated from the surrounding tissues. At her last visit to the clinic, the child showed a recurrence of the swelling at the base of the left side of the neck. It was then learned that the child had entered another hospital for a period of observation. Information from that source showed that the disorder was also diagnosed as that of neurofibromatosis. Of interest is the fact that at this time reentgenograms of the various bones revealed many exostoses, some of which were associated with the tumor masses. Roentgen therapy was given the tumors diminishing in size.

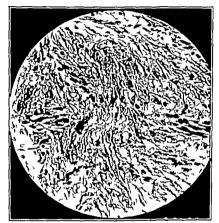


Fig. 5 —Photomicrograph of section of blopsy specimen. Note the thick interlacing fibrous bands and the fine reticular network.

Comment—Case 2 is one of neurofibromatosis in a girl of four years, and is presented because of the unusual character and distribution of the outaneous lesions and because of the lack of constitutional symptoms. The history was that of the development of large indurated masses in the cervical pectoral, scapular, lumbar, and pelvic regions of the body. These swellings were subject to marked fluctuations in size. Biopsy revealed the characteristic pathologic changes of neurofibromatosis. Subsequent roentgenographic examinations showed beginning asseous changes.

### BOURNEVILLE'S TUREROUS SCLEROSIS

Closely related to von Recklinghausen's neurofibromatosis, is the disorder which is known as tuberous sclerosis, a fairly rare congenital

malformation of ectodermal derivation, also affecting the brain, skin, and other organs of the body, and being associated invariably with epilepsy and feeblemindedness. It is sometimes known as "epiloia," a name proposed by Sherlock<sup>17</sup> in 1911. This term has been objected to by Babonneix<sup>18</sup> on the grounds that Sherlock merely redescribed and renamed the clinical picture of Bourneville's tuberous sclerosis

Tuberous sclerosis was first described by Bourneville<sup>10</sup> in 1880. He reported the pathologic changes occurring in the brain of a three-year-old epileptic girl who presented clinically signs of ariested physical development, hemiplegia, idiocy, and "acne rosacea and pustulosis of the face" At necropsy islets of hypertrophic sclerosis were found distributed over the cerebral hemispheres. The brain showed also an anomaly of the olivary bodies. Shortly after, Bourneville, on collaboration with Brissaud, described another case in a four-year old boy who suffered from convulsions. Autopsy revealed similar sclerotic lesions of the cerebral convolutions, in addition to a large hemorrhage in the right frontal lobe, arterial anomalies, and a congenitally malformed heart. However, it remained for Bundschuh<sup>21</sup> and for Bielschowsky and Gallus<sup>22</sup> to describe independently the minute histo logic alterations occurring in the tumors of the brain in tuberous sclerosis.

Of interest are the cutaneous manifestations of tubeious sclerosis, the warty nodules occurring on the face and known as "adenoma sebaceum" or "nevus multiplex of Pringle" In 1890, Pringle23 re ported in a number of patients the presence of "indolent, firm, whitish. or vellowish, sago-grain-like, solid papules or little tumors, imbedded in the skin at different depths, or projecting from it intermingled with these lesions and transgressing their limits in every direction, especially over the cheeks towards the ears, are innumerable capillary dilatations and stellate telangiectases" He recognized two elements in the face lesions, the one, a familiar, transitory form of "rosacea," and the other, an unfamiliar, permanent, neoplastic condition of the sebaceous glands, nevoid in character. He also noted that the eruption appeared to occur in subjects generally mentally below par Pringle grouped these cases under the name of "adenoma sebaceum," but he gave due recognition to the fact that in 1885 Balzer24 proposed the name in reporting a similar type of eluption of the face He also made mention of an unpublished note by Hollopeau on a case of "sebaceous, miliary telangiectatic adenomata" Jadassolin" was the first however, to appreciate the true significance of this anoma lous condition of the skin and showed that it was neither an adenoma tous nor a hyperplastic condition of the sebaceous glands Rather, the lesions belong to the nevoid group of disorders and consist mainly of

hyperplastic connective and vascular tissues. They are part of the widely distributed disorder of tuberous sciences.

That tuberous sclerosis is a widespread systemic disorder, as was adduced by Kufs<sup>20</sup> in 1913 is evidenced by the fact that at autopsy gross abnormalities, such as cysts and tumors are found in other in ternal organs. The kidneys and the heart are most frequently affected although involvement of the pancreas liver and other organs may also occur. As has been reported by Koenen,<sup>27</sup> the disease may show hereditary and familial tendencies. It may be present at birth or be come manifest in early or even in late childhood. According to Yakovlev and Guthrie<sup>1</sup> it is the most typical and clearly defined of the neurocutaneous syndromes in both its clinical and pathologic manifestations.

## ENCEPHALOTRIGENINAL ANGIOMATOSIS

It is a moot question whether the clinical picture of angiomatosis of the brain with vascular nevi of trigeminal distribution should be included in the so-called group of neurocutaneous syndromes Yakovley and Guthrie' have stated 'Indeed the pathology of the vascular neurocutaneous syndrome at first sight obviously consists of congenital malformation of the blood vessels—a tissue, not of ectodermal but of mesodermal derivation. The authors present evidence however in favor of the neurogenic (ectodermal) origin of this vascular anomaly They are of the opinion that " the blood yes sels of the nervous system, of the skin, of the retina and also certain of the glandular organs are the tissues of election for angiomatosis as compared, for example, to tissues of nonectodermal origin, such as bone and muscle ' The distribution of the nevi corresponds, further more, apparently with zones of sympathetic innervation suggesting that the vascular defect may have its origin in some maldevelopment of vasomotor origin. This fact receives added weight from the stud ies on the capillary circulation of the skin by Jaenschas who believes that the development of cutaneous capillaries is dependent in great degree upon the time of melanization of the nerves and the differentia tion of the cerebral cortex The work of Weber 19 has shown also that the telangiectatic 'port wine nevi are apparently neurogenic in nature It should be emphasized that the mesodermal hyperplasia may be present in varying degrees in all three congenital disorders either as an accompanying condition or overshadowing entirely the ectodermal malformation

In their monograph on tumors arising from blood vessels of the brain Cushing and Bailev<sup>10</sup> state that these vascular newgrowths may be divided into two major groups, the augmomatous malformations and the augmomatous or true neoplasms of blood vessel elements. The augmotomatous malformations are due to some defect of develop

ment and contain traces of compressed nerve between their vascular loops, thereby differentiating them from the blood vessel tumors proper, the angioblastomas, which are composed solely of mesodermal tissue. Angiomatous malformations may be predominantly capillary (telangicetatic), venous (angioma venosum), or arteriovenous (angioma arterialis) in their structure. Capillary malformations may occur in various parts of the brain, such as deep in the brain stem, and seldom give rise to symptoms, whereas the venous and arteriovenous angiomas are primarily surface lesions of the cerebral hemispheres, occasionally the hindbiain, and are often provocative of epileptiform seizures. At times the angiomatous newgrowth extends with its apex toward the ventricle

The venous angiomas are of interest in that they may be associated with nevi in the region of the distribution of the trigeminal nerve, a fact of importance in the early recognition of this form of vascular lesion, as compared with arterial angiomas whose presence are difficult of detection unless they are accompanied by an audible bruit or the secondary effects of aneurysmal communications giving rise to enlargement of extracranial vessels. At times, venous angiomas are associated with aneurysmal lesions and occasionally with unilateral exophthalmos. In recent years, Weber, 1 Dimitri, 2 Marque, 3 as well as others, have described cases in which congenital trigeminal nevi were found to be associated with calcified homolateral angiomas of the brain, usually in the occipital area. The majority of the cases occurred in young children in whom epilepsy, mental defect, and unlateral buphthalmus (or glaucoma) were outstanding features

As has been previously stated, the angioblastomas are true vascular neoplasms and are to be clearly differentiated from the angiomatous malformations. According to Cushing and Bailey, angioblastomas are rarely, if ever, accompanied by nevi. They are usually found in the cerebellum, occasionally in the medulla oblongata or in the cord, and they may be either cystic or solid in structure. They were first described in 1926 by Lindau<sup>34</sup> who recognized their true nature while making a study of cysts of the cerebellum. Microscopically, the angioblastomas show a sharp demarcation between the tumor proper and the surrounding nerve tissue and exhibit a marked tendency toward cyst formation. Lindau found also that the angioblastomas are frequently accompanied by concomitant malformations or tumors of so matic organs, such as cysts of the kidneys and pancreas. In addition there may occur vascular newgrowths of the retina

The angiomas of the retina alone have long been known by ophthalmologists under the name of von Hippel's disease 3. However, they were really first recognized in 1894 by Treacher Collins 56 who described two cases, in brother and sister, presenting peculiar vascular newgrowths affecting the retinal structure of both eyes Collins

wrote that "It was made up of a plexus of numerous very thin walled blood vessels and there are in it cystic spaces. It may therefore, best be described as a capillary nevus, which in places has under gone cystic degeneration." According to Lindau 125 per cent of the cases of von Hippel's disease give rise to symptoms of brain complications and 20 per cent of the cases have been found to be familial Møller has called attention to the familial nature of the disease and Rochatr has published his experiences with one family in which the factor of heredity was demonstrable for three generations.

In a recent symposium on the problem of vascular newgrowths of the brain, Lindau<sup>27</sup> stated that

I have adduced good evidence that the subdivisions of the vascular newgrowths into two major groups, angiomatous malformations and hemangioblastomas have been well established and means a great improvement, both elinically and patholog isally Further I have shown that each of these groups includes a general systemic disorder the first a cavernous angiomatosis of the brain and skin, associated with buphthalmus, but no underlying angioma causing eye lesion, and the second, a capillary angiomatosis of the excebellum and the retina with coordinated lesions of the abdominal organs. Thus both these systemic disorders, although related and rather alike, clearly differ and as we have never met with a coincidental occurrence of these two conditions in the same family it would be better at the present stage not to mix them up

Case 3 is presented as an example of the clinical picture of calcified cavernous or venous angioma of the brain associated with nevi in the region of distribution of the trigeminal nerve. The pathologic features of this case have been considered elsewhere by Brock and Dyke 40

CASE 8.—8. L., a white boy was born at full term on May 12, 1925 The delivery was normal, there were no convulsions. The mother a multipara, was thirty four years of age, physically normal, and throughout pregnancy had suffered no illustrate. Her first two pregnancies terminated in miscarriages at three months. Subsequently she was delivered of four normal children. The father was thirty nine years of age, and, at about this time was treated surgically for a gastric uleer. The family history was essentially negative.

At birth the infant weighed 7 pounds (8.18 kg) He was nursed for about sixteen months, and in addition, from six months on, received cereals, fresh vege tables, and orange juice daily, but no ced liver oil. At about four months, the infant was able to hold up its head. He sat up erect at six months, and stood up supported at about eight months, but did not pass through either the crawling or creeping stages of motor development. Walking was delayed markedly until about four years of age. The reason for this rotardation will be explained subsequently. The first tooth crupted at five months. Babbling began at six months of age but the development of speech never progressed beyond this rudimentary stage. Early perceptual and social development followed apparently a normal trend. At approximately six months of age the child showed signs of recognising and smiling at the various members of the family. He was also able to distinguish between strangers and friends.

The first period of liness occurred when the infant was nine months of age. He was then admitted to the Beth Israel Hospital with a history of three days' duration, characterized by convulsions and weakness of the right upper and lower extremities On admission, the temperature was 105° F There was drowsiness, nystagmus of both eyes, and clonic contractions of the right side of the body. A nevus was also noticed on the right side of the forehead, but its full significance was not realized at this time. The left ear showed a purulent of this media. The fundi of both eyes appeared to be normal, but it was noted by the ophthalmologist that the infant did not react promptly to the influence of light. A spinal puncture was attempted, but a bloody fluid was obtained. The Wassermann reaction of the blood was negative. With the subsidence of the acute symptoms, the infant showed a complete paralysis of the right upper and lower extremities. After a period of convalescence, he was discharged from the hospital his condition having been diagnosed as that of polioencephalitis

For the next two years the child was observed in the follow up clinic. During this time, he was subject to attacks of convulsions which occurred at irregular intervals and which were accompanied by brief periods of unconsciousness. Oc casionally the child had several convulsive seizures a day, whereas at other times



Fig 6 — Port-wine nevus of the right side of the forehead and face in the regions of distribution of the first and second branches of the trigeminal nerve.

many weeks intervened between attacks. He was irritable, restless, and slept poorly He lacked urinary control and soiled himself frequently. General motor and manipulatory control was greatly retarded. The weakness of the right upper and lower extremities showed only slight improvement. Apparently, he understood gestures and spoken commands, and he was amenable to discipline. It was also observed that although he reacted to stimulation from bright lights, his sense of perception was poor. It is interesting to note in this connection that improvement was noted in tactile sensitivity and in the appreciation of the attributes of space. Hearing appeared to be normal.

At six and one-half years of age, the boy was readmitted to the hospital in order to ascertain whether the nevus of the face was associated with a similar vascular lesion of the central nervous system. He now weighed 56 pounds (254 kg) and was 43½ inches (1105 cm.) in height. The circumference of his head was 19½ inches (495 cm.) and that of his chest 28 inches (711 cm.). He was well nourished, had good subcutaneous fat and the mucous membranes were of good color. With the exception of the paralyzed limbs, the musculature was firm. His general attitude and behavior was that of the idiot. In bed, he tossed from side to side, hitting

his head or face with his hands or holding his flugers in his mouth. He uttered peculiar, meaningless sounds. It was impossible to attract or to hold his attention. When erect his weight was thrown upon the right lower extremity his right foot was held everted. The right hip was flattened and there was a compensatory scoliosis of the lumbar spine to the left side. When assisted he walked by stepping forward on the left foot, then dragging the right foot up to meet it.

The skin was moist and coarse and showed a normal growth of lanugo hair. The hair of the scalp cycbrows and cyclashes was straight coarse and medium brown. It may be noted here that the nails of the fingers and of the toes were normal. The head appeared to be smaller than normal and was definitely fiattened on the left side posteriorly. The right side of the face was larger than the left side. On the right side of the forchead there was seen a large raised portwine news vivid red in hue and irregularly oblong in shape measuring approximately 11 centimeters in length and 4 centimeters in width (Fig. 6). It began just beneath the hair line and ran obliquely downward and inward to the bridge of the nose then spread out irregularly over the right upper cyclid. A similar but smaller news of irregular shape was also present on the right side of the upper lip and an additional one of oval shape and about 5 centimeters in its longest diameter on the left vertex area of the scalp.

The right palpebral fissure was narrower than the left. The pupils were regular nearest normally to light. The evergrounds could not be examined properly The ears were normal. The nose was fluttened at the bridge, its base was broad. There was no obstruction to masal breathing. The lips were thickened, but the vermillon borders were well defined. The incisor teeth of the upper jaw protruded prominently the lower jaw receded markedly. Ten permanent teeth had crupted and of these, all four first molars showed advanced caries. The enamel was fair. All remaining deciduous teeth showed marked disintegration the stumps being staned brownish black. The tongue was normal and protruded in the midline. The neck was normal. There was no lumphadenopathy.

The chest was symmetrical both nipples were normal. The heart and lungs were normal. Veither the liver nor spicen was palpable. No abdominal masses were present. The genitals were normal in size and the testicles fully descended. Both the right upper and lower extremities showed spastic paralysis and considerable muscular atrophy. However the fingers of both hands were fined and could be extended backwards easily. There was definite shortening of the paralyzed limbs. All deep reflexes were hyperactive on the right side. The right abdominal and cremasteric reflexes were diminished and there was a right-sided Babinski reversal, as well as a prolonged ankle clonus. The skin was hyperactivetic

In view of the history of convulsions progressive mental deterioration and physical signs of central nervous system involvement together with the presence of the extensive nevus on the forchead a clinical diagnosis was made of angiomatous tumor of the brain associated with a nerus of the forchead in the region of the distribution of the trigerninal nerve. Encephalography substantiated the diagnosis (Figs. 7 A B). The erminal cavity was normal. There were no evidences of in orease in intracranial pressure except that the floor of the middle fossa was somewhat depressed and narrow. The solia turcien was small. There was no diastasis of the sutures or of the fontanelles. The cerebral pathways were normal in size but were slightly diminished in number they extended well forward over the frontal area on the right side but were obliterated on the left side. There was defective outlining of the ventricles and on the left side a porenerphalic cyst communicated with the ventricle. The cranial contents were shifted to the left side. The basal elsterns could not be visualized except for an area in the region of the elsterns



B

Fig. 7-A Encephalograms showing the linear calcific deposits in the blood vessels of the right occipital lobe, as well as the porencephalic cyst on the left side. Note the shifting of the cranial contents to the left side,

pontis. There were irregular linear calcifications extending from the region of the lambdold suture to that of the sella turcica. These calcifications were apparently in the blood vessels of the occipital lobe of the brain.

Comment—Case 3 occurring in a boy six and one-half years of age, is illustrative of the encephalotrigeminal variety of vascular neurocutaneous syndrome. Outstanding in the history is the cerebral injury suffered by the boy at nine months of age, leading to right sided hemi plegia, subsequent mental defectiveness, and the frequent occurrence of epileptiform seizures. Clinically, the boy showed an extensive "port wine" nevus of the right side of the forehead and face. Encephalography revealed calcific deposits in the right occipital lobe of the brain, as well as a porencephalic cyst of the left side.

# SUMMARY

Attention is directed to a group of three unusual congenital disorders to which surprisingly little reference has been made in the pediatric literature. The disorders are von Recklinghausen's neurofibromatosis, Bourneville's tuberous sclerosis, and angiomatosis of the brain associated with vascular nevi in the region of the distribution of the trigeminal nerve. All three conditions have been classified in the general category of neurocutaneous syndromes, after the suggestion of French observers. Recently, Yakovlev and Guthrie' have proposed that the diseases be designated by the more descriptive term of "congenital ectodermoses".

All three congenital disorders exhibit marked similarity in their clinical manifestations and in the character and distribution of their pathologic features. Furthermore they involve electively organs, such as the nervous system, skin, ratina and eyeball having their common origin in the ectodermal layer of the developing blastoderm. It should be borne in mind, however, that mesodermal hyperplasia, as is evidenced by the frequent presence of vascular nevi may occur in varying degrees in all three congenital disorders either as a concomitant condition or obscuring entirely the ectodermal malformation

Although all three syndromes show individual and characteristic manifestations they are by no means mutually exclusive. They present signs and symptoms which overlap greatly and which exhibit an impressive range of variability. Of clinical interest is the occurrence of characteristic cutaneous anomalies which are indicative of associated maldevelopments in deeper seated, embryologically related structures such as the peripheral and central nervous systems, and which affect usually the cephalic and caudal ends of the body. The cutaneous manifestations are not purely localized lesions but are the external expressions of widespread systemic maldevelopments which affect visceral as well as somatic structures. This is evidenced by the fact that at autopsy gross abnormalities such as cysts and tumors, are found

in other internal organs. Also of importance in this group of congenital disorders is the involvement of the entire nervous system and, in addition, the frequent occurrence of epilepsy and feeblemindedness. All three neurocutaneous syndromes show, furthermore, definite familial or hereditary tendencies

Von Recklinghausen's neurofibiomatosis is a generalized disease involving primarily nervous tissue in any part of the body with secondary changes in other organs. Characteristically there may occur polypoid tumors of the skin, subcutaneous nodular tumors of the peripheral nerve trunks, lesions of the central nervous system and of the meninges, brownish pigmentation of the skin ("cafe au lait" spots), secondary changes in the skeletal system, and abnormalities of development of visceral structures. The disorder is not seen always in its complete form, various incomplete or abortive forms being present in which only one of the cardinal signs is manifest.

Bourneville's tuberous scleiosis is a fairly rare congenital malformation and it is probably the most typical and clearly defined of the neurocutaneous syndromes in its clinical and pathologic features. It is a widespread disorder showing islands of hypertrophic sclerosis of the cerebral hemispheres, warty nodules of the face, the so called "adenoma sebaceum," and cysts and tumors of internal organs. It is invariably associated with epilepsy and mental defect

The last of the group of neurocutaneous syndromes, is the clinical picture of angiomatosis of the brain associated with vascular nevi in the region of distribution of the trigeminal nerve (encephalotrigeminal angiomatosis) Although, at first sight, it consists of congenital malformation of blood vessels, a tissue of mesodermal origin, evidence is in favor of the fact that it is of neurogenic (ectodermal) origin should be emphasized that vascular newgrowths of the brain are divisible into two major groups, the angiomatous malformations which consist of nervous and vascular tissue, and the angioblastomas or true neoplasms which are composed solely of mesodermal tissue The latter involve primarily the cerebellum and have been known under the name of Lindau's disease They may be either solid or cystic in structure and are accompanied frequently by malformations of visceral organs and vascular newgrowths of the retina (von Hipple's This condition should be clearly disease), but no nevi of the skin differentiated from the angiomatous malformations which are also accompanied by general systemic malformations and by vascular nevi of the skin, as well as buphthalmus (glaucoma) Often the congenital nevi of trigeminal distribution are associated with calcified homolateral angiomatous malformations of the brain, usually of the occipital area

Three case reports have been presented, two of them as illustrations of the varied clinical manifestations of the complicated disorder of von

Recklinghausen's neurofibromatosis, and one of them as an example of angiomatous malformation of the brain in association with vascular nevi of trigeminal distribution

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# DETERMINING APPROPRIATE WEIGHT FOR BODY BUILD\*

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N UTRITIONAL status has long held first place as a measure of health, and rightly so, but modern ideas of judging nutrition are changing rapidly. We know that there is a proper weight range for each child which reflects his optimum development and state of health. This proper weight depends on body build or relative width of the body as well as on height and age

Previous studies by Gray, Franzen, Miles, and others have shown the relationship between various body widths and weight. Gray in 1928 proved statistically that the physical traits most highly correlated with weight were first stature, then bicristal diameter, third age, then bistyloid, then biacromial diameter, and sixth bimalleolar diameter. Gray's material consisted of 810 private school boys aged four to twenty years. He concludes "that weight is best referred to stature, next best to bicristal diameter, only third best to age, while wrist diameter is not worth further consideration. Hence it may be expected that the multiple correlation of weight with stature and bicristal diameter will be better than with stature and age"

The importance of a mathematical appraisal of observed variability was suggested by Faber in 1925. We attempted this in measuring the relationship of width to weight when both were expressed in terms of percentage deviation from the mean for the age sex group

Dublin and Gebhart<sup>5</sup> showed that present standards failed to identify a large proportion of undernourished Italian children. Turner<sup>6</sup> has shown that many underweight children are not malnourished and that a perfectly healthy child may be thin because he has inherited a slender skeleton. He concludes that the skeletal type of the child should be judged as a basis for interpreting the underweight data Clark, Sydenstricker and Collins<sup>7</sup> found that a fairly large percentage of well-nourished native white children were more than 10 per cent underweight according to the Baldwin-Wood tables and they suggest that deviation from average weight need not be a criterion of physical fitness and may not be a matter of ill health or malnutrition. Consideration of body build seems to reconcile these statements with the assumptions upon which the Baldwin-Wood tables are based.

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In Faber's thorough statistical study of the heights and weights of 60,000 San Francisco school children he found that for subgroups consisting of from 400 to 600 members the mode corresponded very closely with the Baldwin Wood standards. For this reason we have based our height weight table for different body builds on the Baldwin Wood table, which established average weight for average build. Then deviation from average build determines deviation from average weight

Faber showed an increase in weight variability with age in both sexes and a marked difference between boys and girls. Our measure ments show a corresponding increase in variability of diameters with age for both sexes and a marked difference in boys and girls begin ning at adolescence.

The width length index of body build as described by Lucas and Pryor makes use of stature and bicristal diameter to designate types of build and also as a basis for weight prediction. The bicristal (or bi iliac) diameter divided by the standing leight multiplied by 100 gives the width length index and is a measure of the relative width of the body. They have followed the technic of Miles and Gray in using firm pressure to get as nearly as possible measurements of the widest flare of the iliac crests. For this purpose sliding anthropometric calipers are the most satisfactory, although spreading calipers may be used. Other body measurements were done as described by Hrdlicka, and adopted by the International anthropometric agreement.

Our width length indices parallel Gray's bicristal stature indices at all ages and for both sexes and are consistently a little smaller. The bicristal diameter appears to be 0.6 cm (0.25 in) less in our series than in Gray's series which may be explained on a basis of superior social economic status in Gray's private school children, since the bicristal diameters obtained by us on our own small series of 300 private school boys are practically identical with Gray's

The bi line diameter can be measured more accurately than chest width or shoulder width because it is not affected by respiratory move ments or changes in posture. The greater accuracy of the pelvic measurement is shown when two or more observers measure the same children consecutively. It was found at the Institute of Child Wel fare for example that for two physicians the average difference in measurement of 112 adolescent children was as follows.

Bi iline 56 girls	2.8	ומתו	or	%	error	$0.99 \pm 0.05$
56 boys	2.6	"				$110 \pm 005$
Bineromial 56 girls	4 "		"	"		ر0 0 ± 149
56 boys	41		4	•	"	$1.86 \pm 0.05$
Lateral Chest 56 girls	3.8	(	4		•	$170 \pm 00$
4 56 boys	4.0		"	•		$2.10 \pm 0.10$

<sup>&</sup>quot;The wooden sliding caliper made by the Marine Compass Company of Hanover, Mass., proved a satisfactory instrument and is far less expensive than the standard anthropometric metal caliper

Todd<sup>10</sup> reported that measurements on the living body need not vary more than 5 to 10 millimeters. Dahlberg<sup>11</sup> reports an average difference in millimeters for various measurements as follows bicristal 164, biacromial 331, and stature 356. Gray reports the difference expected and the difference accepted in his work for various measurements in millimeters as follows bicristal 1-2, stature and biacromial 2-4, and chest measurements 2-10

It seems, then, that the bicristal diameter is the width measurement of choice because it is more constant than any chest measurement, is not affected by respiration, and may be more accurately determined

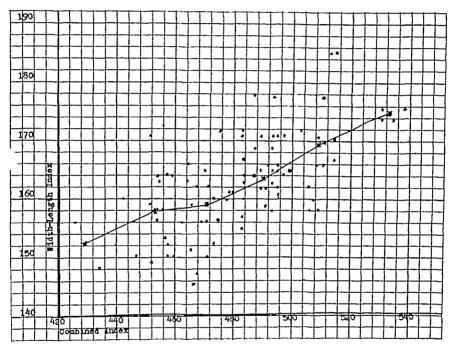


Fig 1 —Width-length index plotted against combined index. One hundred and three girls ages ten eleven and twelve years

Various complicated indices of body build have been advocated, each involving several body measurements of girths and diameters. In order to see what additional information could be had from a more complicated index of build, we have plotted a combined index against the width-length index for 100 boys and 100 girls aged ten to twelve years (See Figs 1 and 2). The combined index consisted of biacromial diameter plus lateral chest diameter, plus anteroposterior chest diameter divided by stature multiplied by 100. A comparison of these chest and shoulder measurements with the single width of hips, each in percentage of standing height, shows that the single width-length index makes practically the same classification of body build as the more complicated one for the group, and is more accurately and more

easily determined. In certain individual instances where there is a lack of symmetry between pelvic and thoracic development there would be differences in the results obtained by these two methods of classification, but we think this occurs infrequently

The relationship between relative width of the body (as measured by the width length index) and body weight was worked out first on 1000 children from Dr Lucas' private practice. It was found that the standard deviation from average weight, referred to the Baldwin Wood table, was approximately double the standard deviation from

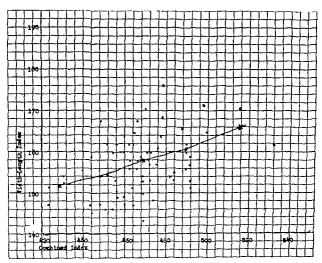


Fig -Width-length index plotted against combined index. One hundred and three boys, ages ten, eleven, and twelve years.

the mean width length index for each age sex group when both were expressed in percentage. The study was then extended to include 2000 public school children in San Francisco Oakland, and San Mateo, 700 clinic patients at the University of California Hospital, 300 clinic patients at Childrens Hospital, San Francisco, 300 private school boys at the Menlo School and Junior College, 200 children in the adolescent study at the Institute of Child Welfare Berkeley, and 60 children studied in a private research by Dr. R. O. Moody at the University of California. Children in the endocrine clinics were excluded as were all others with serious or chronic illnesses.

Our total series of 4560 cases was divided into age sex groups for study. The same relationship between standard deviations from width and weight was found to hold for both the large series and the small series. Those width-length indices which are smaller than the mean distinguish slender-built children and the indices above the mean distinguish broad-built or stocky children. A slender-built child

TABLE I
WIDTH WEIGHT TABLE FOR GIRLS\*
SIX TO SIXTEEN YEARS

			$\mathbf{Six}$	<b>y</b> ear	g					Se	ven	s ears		
-	15 5 6 1	16 5 6 5	17 0 6 7	18 3 7 2	19 6 7 7	20 1 7 9	21 1 cm 8 3 in	16 2 6 4	17 2 6 8	17 7 7 0	19 0 7 5	20 3 8 0	20 9 8 2	21 8 cm 8 6 m
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			Elgh							N	ine y			
	17 2 6 8	18 3 7 2	18 8 7 <b>4</b>	20 3 8 0	21 8 8 6	22 3 8 8	23 4 cm 9 2 in	 18 1 7 1	19 1 7 5	19 6 7 7	21 1 8 3	22 6 8 9	23 1 9 1	24 1 cm 9 5 in
Height in Inches 442 442 442 442 442 442 442 442 442 44	31 32 35 37 38 40 43 44 47 49 52 54 57 59 61	33 34 37 39 41 43 45 47 50 52 55 58 61 62 65	34 36 38 40 42 44 47 49 51 54 57 60 63 65	37 39 42 44 46 48 51 53 56 59 62 65 68 70 73	40 41 46 48 50 52 55 57 61 64 67 70 73 75	41 44 47 49 51 53 57 59 62 66 69 72 75 78 81	43 46 49 51 53 56 59 62 65 69 72 76 79 81	37 38 40 43 44 47 49 52 54 57 59 62 68	39 41 43 45 47 50 52 55 58 61 62 66 69 72	40 42 44 47 49 51 57 60 63 65 68 71 75	44 46 48 51 53 56 62 65 68 70 74 77 81	48 50 52 55 57 61 64 67 70 73 80 83 87	49 51 53 57 59 62 66 69 72 75 78 82 85 90	51 53 559 62 659 72 76 79 81 86 89
	18 8	19 8 7 8	Ten 20 6 8 1	year 22 1 8 7	23 6 9 3	24 4 9 6	25 4 cm 10 0 in	19 6 7 7	20 9 8 2	21 6 8 5	23 1 9 1	24 6 9 7	25 4 10 0	26 7 cm 10 5 in
Height in Inches 48 450 12 25 25 25 25 25 25 25 25 25 25 25 25 25	7 4 40 43 45 48 49 52 55 57 60 64 67 69 72	43 45 48 51 52 55 59 61 64 68 71 73 76	44 47 50 52 54 57 61 63 66 70 74 76 78 82	48 51 54 57 59 66 68 72 76 80 82 85	52 55 58 62 64 67 71 73 78 82 88 88 92	53 57 60 63 669 73 75 80 84 89 91	56 59 63 67 69 72 77 79 84 88 93 95 98 103	43 45 49 51 53 55 58 60 64 67 71 74 78 82 86	45 48 52 54 56 59 61 64 68 71 75 79 83 87	47 50 54 56 58 61 64 66 70 74 78 81 86 90	51 54 59 61 63 66 69 72 76 80 84 88 93 97 102	55 58 64 66 68 71 74 78 82 86 90 95 100 104	57 60 66 68 70 73 77 80 84 89 93 97 103 107	59 63 69 71 73 77 80 84 88 93 97 102 108 112 118
•77	eight	in p	ounde	iw) e	thou	t clo	hing)							

has small bones and should weigh less than a broad built child of the same age and height. The width length index measures the bony framework or body build and provides the basis for calculating the deviation from average weight

TABLE I-CONT'D

			[Acj.	e ye						Thi	rteem	Tes:	,	
	70 G	21.6 8 5	2.3 8.8	4 1 9 5	5 9 10 2	5.6 10.5	109 n.	1 3 8 4	8 9	3.3 9.2	5 i 9 9	26 9 10 6	27 6 10 9	*89 cm 114 in.
[fight   Inches	50 53 54 56 58 61 67 71 74 78 78 97 98	53 56 58 60 61 65 69 71 75 79 81 88 9 97 100	55 58 60 62 64 67 71 74 86 91 95 100 104	60 63 65 67 69 73 77 80 84 88 93 98 103 108 112	65 68 70 72 74 79 83 86 90 95 100 105 111 116 120 125	67 70 72 74 77 81 85 89 93 97 103 108 114 119 124	70 73 76 78 80 85 89 97 102 104 113 125 129	58 60 63 669 72 76 80 81 88 91 93 100 103	61 63 67 70 73 77 80 85 88 93 97 106 109 113	64 65 69 73 76 79 83 88 9 96 100 105 109 113 117	69 71 75 79 82 86 90 104 108 113 118 12 1_6 129	74 77 81 85 88 93 10° 106 112 116 121 117 131 135	77 9 83 88 91 95 100 115 110 115 119 125 130 135 143	80 82 87 92 95 100 101 110 115 120 1 31 131 146 149

		F	ourte	en y	enra					Fi	teen	year		
	1 8 8.6	23 1 9 [	3 9 9 4	25.6 10 1	27 3 10 B	28 l 11 t	29 4 cm 11.6 in	2_ 1 8 %	21 6 9 3	4 4 9 6	26 10.3	28.0 11 0	28 8 11 3	10.0 cm. 11 8 in.
1 68 2 69	64 68 7 77 79 83 87 90 95 97 100 103 103 111 111	68 7 7 81 84 88 9 96 98 103 106 109 115 117 119 110	70 75 79 84 87 92 95 99 106 110 113 118 1 123	76 81 86 91 94 99 103 107 110 115 119 122 128 131 133	8 87 93 98 101 106 111 115 118 1 4 128 131 138 141	84 90 95 101 104 114 118 12 7 137 133 141 145 147 148	88 94 100 105 109 115 119 124 127 133 141 148 151 151	6 79 81 87 89 94 96 96 101 104 112 114 115	\$0 84 88 92 95 99 102 105 107 170 115 121 121 122 124	83 87 91 95 98 103 105 108 111 114 119 123 1 26 128	90 94 98 103 106 111 114 117 120 1_3 129 135 135 136 138	97 101 105 111 114 119 123 1 6 129 132 159 145 146 148	100 104 108 114 117 123 126 129 133 136 143 147 149 150 152	104 109 113 119 1 5 1 8 132 135 135 142 142 144 154 157 157

			2	lixte	n ye			
		22.9 9,0	4 1 9 5	24 9 9 8	26.6 10 5	28 4 11.2	79 2 11.5	30.5 cm. 1 0 in
_	59	74	79	81	11	95	97	102
	60	79	84	87	91	101	104	109 [17
	61 62	85 89	90 94	93 97	101	113	112	121
	63 64	94	99	103	111	113	1 - 3	128
	64	. 97	101	106	115	124	1.7	133
	66	101 106	111	111	120	129	133	139 146
r	67	111	118	122	132	142	146	153
존	68	114	121	125	135	145	149	156
٤.	69 70	119	126	13 L 132	141 143	151	156	163 165
	71	16	133	138	149	160	165	17
ť	7	179	137	14	153	164	169	177
Height I Inches	73 74	134	142	146 150	158	170 174	174 179	182 187

Direct on T ke so at no rest birthday and height at meanwal lock. Measure the ba-iliac diameter and much it with the secarest diamet for the proper as above along the top of the table. Appropriate weight for build it read for the green he ske at that width.

For the convenience of physicians we have constructed Tables I and II showing appropriate weights for body build based on the two physical traits, height and bicristal diameter, which Dr Gray found correlated most highly with weight, and taking into consideration age which correlated third We have called these Width-Weight tables The Baldwin-Wood table was used to determine average height and

TABLE II
WIDTH WEIGHT TABLE FOR BOYS\*
SIX TO SIXTEEN YEARS

15 7 6 2	167 66	81x 17 2 6 8	year 18 5 7 3	19 8 7 8	20 3 8 0	21 3 cm 8 4 in	16 6	2 4	17 3 6 8	18 0 7 1	19 3 7 6	years 20 6 8 1	21 3 8 4	22 4 cm 8 8 m
26 27 28 30 31 32 35 37 38 40 42 44 46	28 29 30 32 33 34 37 39 41 43 44 47 49	29 30 31 33 34 36 38 40 42 44 46 51	32 33 34 36 37 39 42 44 46 48 50 55 55	35 36 37 39 40 41 46 48 50 52 54 57 59	36 37 38 40 41 44 47 49 51 53 56 59 61	38 39 40 42 43 46 49 51 53 56 62 63	33333444	1 2 5 7 8 0 3 4 7 9 1	32 33 34 37 39 41 43 45 47 50 52 54 57	33 34 36 38 40 42 44 47 49 51 54 56	36 37 39 42 44 46 48 51 53 56 59 61 64	39 40 41 46 48 50 52 55 57 61 64 66 69	40 41 44 47 49 51 53 57 59 62 66 68 71	42 43 46 49 51 53 56 59 62 65 69 71 74
17 2 6 8	18 3 7 2	Eigh: 18 8 7 4	20 3 8 0	21 8 8 6	22 3 8 8	23 4 cm 9 2 in	18 7	1	19 1 7 5	19 6 7 7	ine y 21 1 8 3	enrs 22 6 8 9	23 1 9 1	24 1 cm 9 5 in.
31 32 35 37 38 40 43 44 47 49 52 54 57 59	33 34 37 39 41 43 45 47 50 52 58 61 62 65	34 36 38 40 42 44 47 49 51 54 57 60 63 67	37 39 42 44 46 48 51 53 56 62 65 68 70	40 41 46 48 50 52 55 57 61 64 67 73 75	41 44 47 49 51 53 57 59 62 66 67 72 75 78	43 46 49 51 53 56 59 62 65 69 72 76 79 81 85	3 4 4 4 4 4 5 5 5 6	803479247925	39 41 43 45 47 50 52 55 61 62 66 69 72	40 42 44 47 49 51 54 57 60 63 65 68 71 75	44 46 48 51 53 56 59 62 65 68 70 74 77 81	48 50 52 55 57 61 64 67 70 73 75 80 83	49 51 53 57 59 62 669 72 75 78 82 85 90	51 53 56 59 62 65 69 72 76 79 81 86 89
18 3 7 2	19 3 7 6	Ten 20 1 7 9	year 21 6 8 5	23 1 9 1	23 9 9 4	24 9 cm 9.8 in	19 7	0	20 0 7 9	20 8 8 2	22 3 8 8	23 8 9 4	24 6 9 7	25 6 cm 10 l 10
40 43 44 47 49 52 54 57 60 63 66 69 72 75	43 45 47 50 52 55 61 63 67 70 73 76	44 47 49 51 54 57 60 63 65 69 72 78 82	48 51 53 56 59 62 65 68 71 75 78 82 85 89	52 55 57 61 64 67 70 71 77 81 88 92 96	53 57 59 62 66 69 72 75 79 83 86 91	56 59 62 65 69 72 76 79 82 87 90 95 98 103	5 6 6	7 9 2 4 7 7 0 3 3 6 9 2 7 6 7 8	47 50 52 55 58 61 67 70 73 77 80 83 88 92	49 51 54 57 60 63 65 69 73 76 79 83 86 91	53 56 59 62 65 68 71 75 79 82 86 90 93 98 103	57 61 64 67 70 73 77 81 85 88 93 97 100 105	59 62 66 69 72 75 79 83 88 91 95 100 103 108	62 65 69 72 76 79 82 87 92 95 100 104 108 1113 1119
	6 2 26 27 28 30 31 32 35 37 38 40 44 44 46 46 46 47 47 49 49 49 49 49 49 49 49 49 49 49 49 49	6 2 6 6 26 28 27 29 30 32 31 33 32 34 35 37 37 39 38 41 40 43 44 47 46 49 17 2 18 3 6 8 7 2 31 33 32 34 44 47 46 49 17 2 52 55 54 58 57 61 68 72 31 33 32 34 44 47 47 50 49 43 41 47 47 50 48 55 57 62 61 65 65 67 73 77 75 79 79	10 7 16 7 17 2 6 2 6 6 6 8 29 27 29 30 28 30 31 31 33 34 35 37 38 41 42 44 47 49 46 49 51 2 18 3 18 8 6 8 7 2 7 4 4 4 4 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 4 9 4 7 5 0 5 1 6 6 6 6 7 6 7 7 9 8 2 8 2 8 2 8 2 8 2 8 2 8 2 8 2 8 2 8	15 7 167 172 185 6 2 66 68 7 26 28 29 32 27 29 30 33 28 30 31 34 30 32 33 36 39 31 37 34 36 39 35 37 38 42 37 39 40 44 38 41 42 46 40 43 44 46 50 44 47 49 53 46 49 51 55  Eight yen 17 2 18 3 18 8 20 3 6 8 7 2 7 4 8 0 31 33 34 36 39 35 37 38 42 44 46 50 44 47 49 53 36 8 7 2 7 8 8 20 31 33 34 36 39 35 37 38 42 44 46 50 44 47 49 53 46 49 51 55  Fight yen 17 2 18 3 18 8 20 3 3 3 4 3 6 39 3 5 5 7 7 8 8 42 3 1 3 3 4 3 6 39 3 5 5 7 7 8 6 8 7 7 7 8 8 7 7 8 8 7 7 8 8 7 7 8 8 7 7 8 8 7 7 8 8 7 7 8 8 7 7 8 8 7 7 8 8 7 7 8 8 7 7 8 8 7 7 8 8 7 7 8 8 7 7 8 8 7 7 8 8 7 7 8 8 7 7 8 8 8 7 7 7 8 8 8 7 7 7 8 8 8 7 7 7 8 8 8 7 7 7 8 8 8 7 7 7 8 8 8 7 7 7 8 8 8 7 7 7 8 8 8 7 7 7 8 8 8 7 7 7 8 8 8 7 7 7 8 8 8 7 7 7 8 8 8 7 7 7 8 8 8 7 7 7 8 8 8 7 7 7 8 8 8 7 7 7 8 8 8 7 7 7 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 7 8 8 8 8 7 7 8 8 8 8 7 7 8 8 8 8 7 7 8 8 8 8 7 7 8 8 8 8 7 7 8 8 8 8 7 7 8 8 8 8 7 7 8 8 8 8 7 7 8 8 8 8 7 7 8 8 8 8 7 7 8 8 8 7 7 8 8 8 7 7 8 8 8 7 7 8 8 8 7 7 8 8 8 7 7 8 8 8 7 7 8 8 8 7 8 7 8 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8 8 7 8	15 7 167 172 185 198 6 2 66 68 7.5 78 26 28 29 32 35 27 29 30 33 36 28 30 31 34 37 30 32 33 36 39 41 35 37 38 42 46 37 39 40 44 48 32 42 44 46 50 54 44 47 49 53 57 46 49 51 55 59  Eight years 17 2 18 3 18 8 20 3 21 8 6 8 7 2 7 4 8 0 8 6 8 7 2 7 4 8 0 8 6 8 7 2 7 4 8 0 8 6 31 33 34 37 40 32 34 36 39 41 35 37 38 42 46 44 47 49 53 57 46 49 51 55 59  Eight years 17 2 18 3 18 8 20 3 21 8 6 8 7 2 7 4 8 0 8 6 8 7 2 7 4 8 0 8 6 8 7 2 7 4 8 0 8 6 8 7 2 7 4 8 0 8 6 8 7 2 7 6 7 9 8 5 9 1  40 43 44 48 52 43 45 47 51 55 44 47 49 53 57 47 50 51 56 61 49 52 54 59 64 52 55 57 62 67 54 58 60 65 70 57 61 63 68 73 59 62 65 70 75 61 65 67 73 79  Ten years 18 3 19 3 20 1 21 6 23 1 7 6 7 9 8 5 9 1  40 43 44 48 52 43 45 47 51 55 44 47 49 53 57 75 61 63 68 73 79  40 43 44 48 52 43 45 47 51 56 61 65 67 73 79  54 58 60 65 70 75 61 63 68 73 76 79 85 91  40 43 44 48 52 43 45 47 51 55 54 58 60 65 70 57 61 63 68 73 59 62 65 70 75 61 63 66 70 72 28 84 69 71 76 82 88 72 76 78 85 92 75 79 82 89 96	15 7 167 172 185 198 203 6 2 66 68 75 78 80  26 28 29 32 35 36 27 29 30 33 36 37 28 30 31 34 37 38 30 32 34 36 39 41 32 34 36 39 41 44 35 37 38 42 46 47 37 39 40 44 48 49 38 41 42 46 50 51 40 43 44 48 52 53 42 44 46 50 54 44 47 49 53 57 59 46 49 51 55 59 61  Elght yenrs  17 2 18 3 188 20 3 21 8 22 3 6 8 7 2 7 4 8 0 8 6 8 8  31 33 34 36 39 41 44 35 37 38 42 46 47 37 39 40 44 48 52 53 42 44 46 50 54 44 47 49 53 57 59 61  20 20 20 20 20 20 20 20 20 20 20 20 20 2	15 7 167 172 185 198 203 213 cm 62 66 68 75 78 80 84 in  26 28 29 32 35 36 38 27 29 30 33 36 37 39 28 30 31 34 37 38 40 30 32 33 36 39 40 42 31 37 34 36 39 41 44 46 35 37 38 42 46 47 49 37 39 40 44 48 52 53 56 44 44 46 50 54 56 58 44 47 49 53 57 59 61 31 33 34 37 40 41 32 34 36 39 41 44 46 35 37 38 42 46 60 63 44 47 49 53 57 59 62 46 49 51 55 59 61 63  28 29 32 32 38 36 39 41 44 36 36 37 38 42 46 67 49 37 39 40 44 48 49 51 38 41 42 46 50 54 56 58 44 47 49 53 57 59 62 46 49 51 55 59 61 63	15 7 167 172 185 198 203 213 cm 166 2 66 68 7.5 78 80 84 in 62 82 93 32 35 36 38 37 39 38 38 30 31 34 37 38 40 42 33 31 33 36 39 40 42 33 31 33 36 39 40 42 33 31 33 36 39 41 44 46 33 35 37 38 42 46 47 49 37 38 41 42 46 50 51 53 44 47 49 53 57 59 62 44 47 49 53 57 59 61 63 58 41 42 46 47 49 51 55 59 61 63 58 41 42 46 49 51 55 59 61 63 58 41 42 46 49 51 55 59 61 63 58 41 42 46 49 51 55 59 61 63 58 41 42 46 50 51 51 53 44 44 47 49 51 55 59 61 63 58 41 42 46 50 51 51 53 44 44 47 49 51 55 59 61 63 58 41 42 46 49 51 55 59 61 63 58 41 42 46 50 51 51 53 44 44 47 49 51 55 59 61 63 58 41 42 46 50 51 51 51 51 51 51 51 51 51 51 51 51 51	15 7 167 172 185 198 203 213 cm 64  26 28 29 32 35 36 38 30  27 29 30 33 36 37 39 31  28 30 31 34 37 38 40 32  30 32 33 36 39 40 42 35  31 35 34 36 39 41 44 46 38  35 37 38 42 46 47 49 40  38 41 42 46 50 51 53 44  40 43 44 48 52 53 56 47  44 47 49 53 57 59 62 51  46 49 51 55 57 61 63 51  57 61 63 68 73 75 99 62  47 50 51 56 61 62 65  57 61 63 68 73 75 99 62  40 43 44 48 52 53 56 47  44 47 49 53 57 59 62  57 61 63 68 73 75 99 62  57 61 63 68 73 75 99 62  57 61 63 68 73 75 99 62  58 60 65 70 72 76 62  59 62 65 70 77 78 81 85  78 79 82 89 96 99 103 83  87	10 7 167 172 185 198 203 213 cm 162 173 662 66 68 75 78 80 84 in 64 68 26 26 68 75 78 80 84 in 64 68 27 29 30 33 16 37 39 31 33 32 83 30 32 33 36 39 40 42 35 37 39 31 33 31 33 34 37 38 40 32 34 36 39 40 42 35 37 39 31 33 31 33 34 37 40 41 43 37 38 40 41 43 37 39 40 44 48 49 51 43 44 46 38 41 37 38 42 46 47 49 40 43 38 41 42 46 50 51 53 44 47 40 43 44 48 52 53 56 47 50 44 47 49 51 55 59 61 63 54 57 38 42 46 47 49 40 43 38 41 42 46 50 54 56 38 49 52 44 47 49 51 55 59 61 63 54 57 38 42 46 47 49 40 43 37 39 40 44 48 52 53 56 47 50 44 47 49 51 55 59 61 63 54 57 38 42 46 67 79 85 91 94 98 81 47 50 47 50 47 50 51 55 57 59 62 51 54 47 50 47 50 51 55 57 59 62 51 54 57 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 51 50 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80 88 89 91 95 76 60 60 70 72 76 60 77 70 70 80 88 89 91 9	12 7 16 7 17 2 18 5 19 8 20 3 21 3 cm	15.7 16.7 17.2 18.5 19.8 20.3 21.3 cm	15 7 167 172 185 198 203 213 cm 62 66 66 68 7.7 78 80 84 un 64 68 71 76 81  26 28 29 32 35 36 38 30 32 33 34 37 40 27 29 30 33 36 37 39 31 33 43 74 40 30 312 33 316 39 40 42 35 37 38 42 46 31 31 31 34 37 40 41 43 37 38 41 42 46 50 315 37 38 42 46 47 49 40 43 44 48 52 53 56 47 50 51 56 61 44 47 49 53 57 39 62 52 55 57 62 67 69 72 59 62 65 70 75 89 81 85  Eleth years  Eleth years  Eleth years  17 2 18 3 18 8 203 21 8 22 3 23 4 cm 18 1 19 1 19 6 21 1 22 6 67 69 72 59 62 65 70 75 81 81 87 87 81 89 41 44 48 85 25 55 56 64 77 50 51 56 61 64 44 47 49 53 57 39 64 69 51 55 57 61 63 68 73 75 79 82 88 94 44 47 49 53 57 59 62 62 65 70 75 75 81 87 81 87 81 87 81 87 81 87 81 81 81 81 81 81 81 81 81 81 81 81 81	10.7 16.7 17.2 118.5 19.8 20.3 21.3 cm

<sup>&</sup>quot;Weight in pounds (without clothing)

weight for each age sex group. The Underweight Reference tables compiled by the American Child Health Association in 1924 were used to determine 7 10 15 per cent under average weight for each age and height. The percentages over average weight were calculated directly from these

TABLE II-CONT'D

			rwei											Jear		
	19 % 7 %	*0 8 8 Z	21.6 8.5	23 1 9 1	24.6 9.7	10.0				20 3 8.0	1 3 8 4	22 i 8 7	23 6 9.3	25 1 9 9	25 9 10.2	26.9 cm. 106 n.
Height in Inches	47 49 52 55 56 63 66 70 77 76 79 81 88 90	50 52 55 59 61 64 67 70 74 78 80 84 88 93 96	51 54 57 61 64 66 69 73 77 80 83 87 92 96 99	56 59 62 66 69 7 75 79 83 87 90 94 107 112	61 64 67 71 74 78 81 85 89 94 97 101 106 11	62 66 69 3 77 80 83 88 92 96 100 104 115 118 124	65 69 72 777 80 84 87 9 96 101 104 109 115 120 124 129			52 558 604 67 70 73 770 84 89 97 99 103	55 59 61 64 68 71 74 78 81 85 89 94 103 105	\$7 61 64 66 70 74 77 80 84 88 9 97 101 106 108	62 66 69 72 76 80 83 87 91 100 105 109 117 1 2	67 71 74 78 82 86 89 94 98 102 108 113 117 124 126 131	69 3 77 80 84 89 92 96 101 105 111 116 120 127 129	77 77 80 84 \$\$ 96 101 103 116 121 126 133 135 141
	21 1	22 3	urte 31	24 9	26 7	<b>27</b> 5	28.7	сm		216	22 9	23.6	25 4	70871 27 2	27 9	29 cm.
	8.3	8.8	91	98	10 5	10 8	113	in.		B.5	90	93	10 0	10 7	110	11.5 n.
54 55 65 7 5 5 9 66 1 62 63 64 65 66 7 5 9 7 1 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	59 60 64 71 74 77 85 89 98 101 1106 1114 119	61 64 68 72 75 79 8 87 99 90 95 99 104 113 118 121 126	65 66 70 75 78 81 85 90 93 103 107 111 112 125 131 135	70 72 76 81 88 9 97 101 116 126 135 141 146	75 78 82 87 95 99 104 119 125 125 142 145 151	78 80 84 90 93 97 102 107 112 117 128 133 146 149 156	81 84 88 947 10 107 1123 128 134 139 146 153 156 169			66 68 7 74 78 83 86 91 95 100 104 111 116 125 128 131	70 72 76 79 83 88 91 91 106 110 113 113 123 133 135 142	7 755 781 86 91 100 105 109 114 118 122 127 137 140 144	78 81 85 893 98 102 108 113 118 123 128 137 142 148 155 158	84 87 95 100 105 116 121 127 138 142 147 152 166 170	86 90 94 103 108 119 1 5 130 141 146 151 163 167 171 174	90 94 98 10 108 113 113 115 131 136 14 148 153 158 164 171 174 179 182
						• • •	3 6 2	xtee	16 7	28 O	8.8	30.0 c				
						2.3 2 8.8	93	9.6	10 3	110	11 3	11.81	_			
			_	5°	1	74 79 85	79 84 90	\$1 87 93 97	88 94 101 105	95 101 109 113	97 104 11 116	102 109 117 1 1				

2.3 216 244 26.2 28 0 8.8 30.0 cm.

8.9 93 94 103 110 113 11.81

69 74 79 84 87 94 101 110 110 110

61 85 90 91 101 109 111 117

62 89 94 97 105 113 116 11

64 97 109 106 111 119 121 128

64 97 109 106 111 119 121 128

64 107 108 108 111 128 129 131 139

65 106 113 111 126 121 131 149

7 67 111 118 12 125 135 145 146 156

8 68 114 121 125 135 145 146 156

8 69 119 127 138 149 156 156

8 69 119 127 138 149 156 157

8 70 121 125 135 145 149 156

8 70 121 125 135 146 156 17

8 71 125 137 141 141 151 161 165

8 72 125 137 141 141 151 179 187

74 13 145 150 162 174 179 187

74 13 145 150 162 174 179 187

Direction The set near est birthd y and belight at nearest fach. Measure the bi-like diameter for the proper se shown loss the top of the table. Appropriate neight is build seal for the given height at that width.

The mean width-length index as calculated for each age sex group in our series was matched with the figures for the average height and average weight for each age sex group on the Baldwin-Wood table.\* The 7 per cent underweight column from the Reference Table was matched with the figure for 7 per cent narrower than the mean of the width-length index for each age sex group, the 10 per cent underweight column was matched with the figure for 10 per cent narrower than the mean, and the 15 per cent underweight column was matched with the 15 per cent narrower than the mean of the width-length index. The over average weight columns were calculated in the same manner

Since it seems cumbersome to print the width-length index with each weight the indices are omitted and only the width measurements are shown. The center width for each age and sex represents the mean of the measurements of the bi-iliac diameter for that age and sex in our series. The other widths are those from which the 7, 10, and 15 per cent variation indices were derived.

The Width-Weight tables offer seven normal weights for each height and age depending on the width of the iliac diameter. Since width measurements should be done next to the skin, the weights in the Baldwin-Wood table and from the American Child Health Underweight reference tables were corrected for clothes by subtracting one pound for heights 38 to 40 inches and two pounds for heights above 40 inches, as suggested in the Baldwin-Wood table. Our table is then a modification of the Baldwin-Wood table, taking width into consideration

To use the Width-Weight table age is taken at the nearest birthday and height at the nearest inch. The actual bi-iliac diameter is matched with the nearest width measurement shown for the proper age sex group at the top of the table and the weight is read for the proper height at that width. Children who deviate very markedly from average, those too tall or too short, too broad or too narrow to be found on the table, should be considered individually

<sup>\*</sup>In preparing Tables I and II showing weight deviation in terms of width deviation the regression formula  $y = (r \frac{\sigma_r}{\sigma_e})x$  was applied as suggested by Dr R. L. Jenkins. When x equals the percentage deviation from the mean width-length index for the age sex group and y equals the percentage deviation from average weight for height age and sex as given in the Baldwin-Wood table application of the formula yields the following values

	A ges	$\mathbf{r}_{\mathbf{x}\mathbf{r}}$	$\frac{\sigma_{\tau}}{\sigma_{x}}$	
Male and Female Male Female Male Female	6 7 8 9 10 11 12 10 11 12 13 14 15 16	0 48 0 63 0 622 0 46 0 51	2 19 1 59 1 45 1 85 2 05	1 051 1 007 0 902 0 951 1 045

It appears then, that (within the limits of the tables presented in this paper) weight deviation varies in direct proportion to width deviation since y equals approximately 1

TABLE III COMPARISON OF OLD AND NEW STANDARDS

	***************************************	MAL DEVIATION		+ 00	87	0.5	-19	+1.5	60-	F 6-	-3.3	-13	90	e e	oi +	+9.5	약	+0.5	+3.7	+3.5		90+	+01	+10.4	90	ec. 67	6.0	181		
	200	TOTAL DEVIATION		0.1	+4.8	+3.5	+13	0	35	9,8-	51	77	+1.7	£.0+	95 CT+	07	+19	8.0+	+3.9	+26	+7 6	-1.8	970-	+10	- 7	9	+4.7	71.6	Total per cent	deviation
1001		1VER.	MINUS	51	5.0	101	88	9 +	5.0	<b>6.</b> ,	<del>†</del> 6	7.0	4 8	7 6	7.0	7.3	٠. ن	6.9	8 9	6+	7.7	7.0	80	7.0	¢1	1.1	7.7			
PERCENTAGE DEVIATION PROM	WEIGHT FOR BUILD	9	CABES	9	1	¢ı	13	2	11	18	11	Ç1	70	13	17	13	18	Ŀ	17	13	18	16	t~	C	4	23	+	207	2 xero dovintion	
CENTAGE D	WEIGHT	AVER.	PLUR DEV	7.9	98	el el	0.0	4.0	es es	£"F	5.0	9 0	7 0	11,0	76	98	ŧ fî	1 +	10 2	7.4	7.3	7 6	80	10 0	G 3	+ 6	7.5		2 xero	
100		2	CASTS	13	æ	77	7	2	13	11	13	ko	15	œ	19	10	15	0	16	13	13	œ	#	-#	11	7		35		
NO		LVFB	MINTER	7.7	0.9	<b>→</b> 00	10.4	8	13.3	0.4	103	9.6	6.6	9.7	9 2	9.3	10.0	7.8	103	11	110	20	11.0	80	61	11.8	*			
PERCENTAME DEVIATION FROM	BALDWIN WOOD WEIGHT	U.N.	CABES	-	CI	3	13	٤ı	33	<u></u> 61	11	đ	જ	10	8	13	o,	30	10	16	61	10	9	¢,	<b>.</b>	+	в	318	6 kero deviation	DOI CHECK TOTAL
CENTAGE D	BALDWIN W	AVER.	PLUS DEV	117	10,8	11.9	11.	8.7	9.7	62	8.1	el el	11.6	9.9	12,3	13,3	13 1	8 3	17	103	18 6	7.0	10,	10.	10.1	2.0	14.1		0 1010	100
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To test the superiority of the new width-weight tables over the original Baldwin-Wood tables the amount of deviation from each weight standard was measured on a series of 531 unselected healthy children. Table III shows the average amounts of deviation above and below the Baldwin-Wood normal and above and below the width-weight normal for each age and sex. Ages were distributed from four to fifteen years and deviations were measured in percentage of the normal

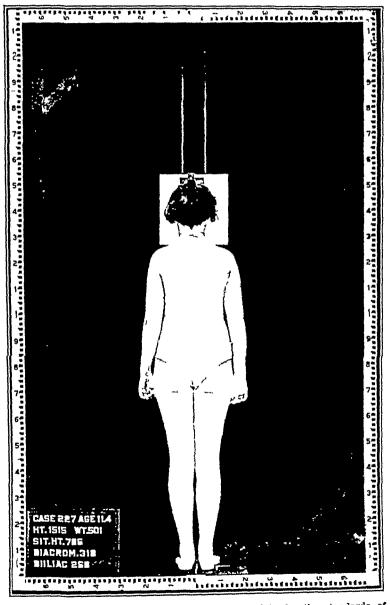


Fig 3—This girl is twent)-three per cent overweight by the standards of the Baldwin-Wood table, but since her width-height index is 107 per cent greater than the average for her age her weight is only 123 per cent above the average for her age height, and skeletal build (The measurements shown on the photograph are in millimeters and hectograms)

The total group of children vary from the new table 481 per cent (0 090 per cent per child) as compared with 715 per cent from the Baldwin Wood (0 135 per cent per child)

For the general population as represented by the 531 unselected children the new width weight table fits 327 per cent better than the Baldwin Wood table

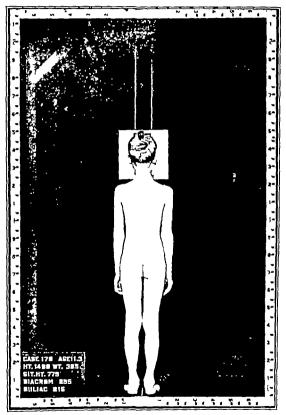


Fig. 4—This boy is fifteen per cent underweight by the standards of the Baldwin-Wood table, but since his width height index is 77 per cent less than the average for his age his weight is only 7.3 per cent below the average for his age, height, age, height, age, height, age, height, age, height, and aksietal build (The measurements shown on the photograph are in millimeters and hectograms).

Width Length Indices (B. 1806 Dumeter in Inches)

	em ınches				
	30 3 12 0			199 196 192 190 186	183 180 178
	$\frac{29}{117}$		201 197	194 191 187 184 182	179 176 174
	29.2 11.5		201 197 194	191 188 184 181 178	176 173 171
	285 112		197 197 194 191	187 184 181 178	173 170 168
	27 9 11 0		199 195 192 189 180	183 190 177 174 171	169 166 164
	27 2 10 7	791	194 190 187 184 181	178 176 171 169 166	164 161 159
	267 105	201 193 193	190 187 183 180 177	174 173 168 166 166	161 158 156
	25 0 10 2	201 197 188 190	186 183 180 177 177	171 168 165 163 160	158 156 153
(8)	25 4 10 0	199 197 191 182 184	181 178 174 171 169	166 163 160 158 158	120
n inches	24 0 9 7	197 193 189 186 178	176 173 170 107 164	161 159 156 153 151	148 146 144
noter	24.1 9.5	197 193 189 183 183 175 175	172 169 166 163 161	158 155 155 170 148	145
Bi iliae Diamoter in	23 <del>1</del>	197 193 180 181 181 171	168 165 163 160 157	155 152 140 117 147	142 140 138
Bi ilia	9 0 0	203 197 197 198 198 198 179 170 170 166	163 160 158 154 154	149 148 145 140	138 135 134
_	22.1	196 193 188 184 180 177 177 170 167 161	178 173 173 147	145	134
	216	192 188 184 180 176 173 160 160 160 160 160 173	1112	141 130 137 134	
	20.0 8.0 8.0	187 183 179 170 172 172 165 165 170 170	151 148 145 143	138 136 133	
	203 80	181 177 173 170 160 160 150 150 150 150 150 150	143 143 137	135	
	10 0	174 170 167 167 157 151 148 145	137 137 135		
	19 0	170 164 162 159 150 150 150 147 144 141	136		
	153	165 162 158 158 156 140 140 148 148 138			
	17.7	ARREAR ARR			
		## ## ## ## ## ## ## ## ## ## ## ## ##		82324	588
	$\ $	перев	Height in I		

TABLE V

MEAN WIDTH LEEGTH INDEXES FOR SCHOOL CHILDREN ARRANGED BY SEX AND AGE

Age in years											
Index Boys	1 9	158	158	158	1.8	157	15,	156	15)	155	154
Girla	159	150	150	19	160	161	162	163	363	104	164

TABLE VI
PERCENTIGE DEVIATION CORRESPONDING TO EACH UNIT OF DEVIATION FROM THE
MEAN WIDTH LENGTH INDEX

WIDTH LENGTH	PERCEN	T DEVIA	TIONS 1	ROM II	FRAGE	NDEX I	OB EAC	II UNIT	OF DEV	IATION
INDEX	1	-	3	+	)	0	1	В	8	10
150 153	0	1.3	20	0.1	3 3	4.0	4 6	5.3	60	66
154 157	0.6	18	1.9	26	8.2	3.9	4.5	51	5.9	64
158 161	0.6	13	1.9	2.5	31	3.7	44	50	5.6	63
162 165	0.6	1.2	1.8	2.4	31	87	4.3	49	5.5	6.1
166 169	0.6	1.2	1.8	24	8.0	3.6	4.2	4.8	54	6.0
170 175	0.6	12	17	28	2.9	8.5	4.1	4 ~	[ 7.2	58

Eraspie The mean width hight index for cleven year-old girls is 161 (Rec Table V) For a girl of this age whose index is 166 the unit deviation is 5 and the percentage of deviation is 5 1 per cent. She is 3 1 per cent broader for her height than the average for girls of her age.

Table IV is included for the convenience of those who are interested in finding the width length index. The bi-liac diameter is found along the top and the standing height in the left hand column. The width length index appears where the two columns intersect.

Mean width length indexes for our 4560 children by age and sex are shown in Table V The width length index for each child should be compared with the mean in this table, his percentage deviation may then be found by consulting Table VI To use this device determine the difference between the child's width length index (found on Table IV) from the mean for his age and sex (found on Table V) Locate this difference along the top line of Table VI Then find the mean width length index for age and sex in the left hand column of Table The percentage deviation appears where the two columns inter This percentage deviation may be read as 8 per cent narrower than average or 12 per cent broader than average for age and sex ' Since percentage deviation in weight from the Baldwin Wood table allowed for body build is equal to the percentage deviation found on Table VI the child who is 8 per cent narrower than average may weigh 8 per cent less than the weight assigned by the Baldwin Wood table for his age and height. The child found to be 12 per cent broader than average may weigh 12 per cent more than the weight assigned on the Baldwin Wood table

In the rare cases where the percentage deviations from the width length index are more than 15 per cent an individual judgment should be made although the principle of the relationship between width and weight is still applicable. If the table were extended to cover wider deviations from average it would become too large and the chances

of maccuracy would be greater since extreme deviations would be based on too few cases The probability curve for deviation of normal persons from zero shows that there is one chance in about 150 of a deviation of 17 per cent and only one chance in about 500 of a deviation of 20 per cent

## SUMMARY

- 1 Nutritional status remains the best single criterion of health
- 2 Relative width of the body, or body build, should be considered in judging appropriate weight for age and sex
- 3 The relationship of body width to weight has been analyzed by mathematical correlation, using the measurements of 4560 school children
- 4 A simple method of measuring body build has been used to help determine appropriate weight
- 5 The four traits found to have the highest mathematical correlation with body weight are combined in new tables of appropriate weights for children aged six to sixteen years
- 6 The new tables fit the general population much better than the Baldwin-Wood tables when deviations from both standards are compared for 531 children

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#### HEREDITARY ATAXTA

## ALLAN PENNY BLOXSON, M D HOUSTON, TEXAS

BROUSSEE gave the name of Friedreich's disease to the symptom complex described by the Heidelberg chincian in 1863. This disease was characterized by onset during childhood, ataxia, loss of the patellar reflex hystagmus, pes equinus a slowly progressive course and its occurrence in members of the same family

The existence of this clinical picture was confirmed in a large number of publications but it was soon found that the disease was not as sharply defined as at first described. Marie described a condition in young adults that had many points in common with the symptom complex of Friedreich, but differed in that there was a later onset, greater uncertainty in the gait the tendon reflexes were present or exagger ated, there were ocular palsies and occasionally atrophy of the optic nerve. The existence of this clinical picture was confirmed by a number of observers and then cases were discovered combining symptoms of both diseases.

Most clinicians have come to the conclusion, in view of these facts, that Friedreich's disease and Marie's cerebellar ataxia can no longer be separated into two distinct groups either clinically or pathologically, and that it is more correct to include both of these conditions under the head of hereditary ataxia with preponderance of the spinal symptoms in some cases and of the cerebellar symptoms in others

The spinal form of hereditary ataxia appears in the first decade of life as a rule, while the cerebellar form shows the first symptoms usually after the age of twenty. However, there is no constant difference between the spinal and cerebellar forms as regards the age when the disease first makes its appearance. The outstanding symptom of the cerebellar form of hereditary ataxia is the uncertainty of the gait. The disturbance of coordination affects not only the walking but also the standing and sitting postures. The motor unrest is not confined to the legs and early involves other portions of the body producing wob bling of the head tremor of the hands, and ataxia of the arms.

Peculiar postures of the feet are often found in the spinal form of hereditary ataxia. The malformations are caused by an over extension of the large toe which may be an early symptom. As a rule it is followed by a further malformation of the foot and clawlike position of the toes. Roentgenograms do not show anomalies of the skeleton.

It is interesting to note that as a rule either the male members or the female members of a family are exclusively attacked. However, there appears to be no difference between the sexes as regards frequency The behavior of the patellar reflex is not constant. As a rule, the patellar reflex disappears early in the spinal form of hereditary ataxia and is exaggerated in the cerebellar form, but there are spinal forms of the disease with exaggerated patellar reflexes and cerebellar forms of the disease with diminished reflexes

When the spinal form of hereditary ataxia has existed for some time there is a scoliosis or kyphoscoliosis, due to the weakness of the spinal muscles

A series of important cerebral symptoms frequently accompany hereditary ataxia. Nystagmus is common in the spinal form and occasionally absent in the cerebellar type. Disturbance of the ocular muscles, such as strabismus, ptosis, and diplopia, have been observed in the cerebellar type. Optic atrophy is frequently present. The pupils are normal

Speech might be compared to the gait in that it is slow and sometimes scanning. The speech defect usually increases with the severity of the disease. The intellect is also impaired in the spinal form. There may be a few infrequent symptoms, such as profuse salivation and forced laughter.

It was formerly thought that in hereditary ataxia there were few if any sensory changes, but in the light of later case reports with anatomic studies this view has been changed

The problem which the disease presents is not so much the distribution of the lesions with the resulting clinical picture as the causation and exact nature of the affection. The following case report is given and the literature briefly reviewed in order to help further determine, if possible, the nature of hereditary ataxia.

## CASE REPORT

M Y, white female child, three and a half years old, was born November 21, 1927 At this time her father was twenty nine years of age and her mother twenty five years of age. There were two older children, a girl of six years and a girl of two years, both apparently well. The mother had one miscarriage at four months between the first and second child

The father's mother at the age of thirty five developed an ataxia and eventually had to be placed in a hospital. The father died a few months after the patient was born

The mother's health was good while she was carrying the patient Birth was normal at full term, and the infant weighed nine pounds and twelve ounces Feed ing had to be supplementary

At the age of five months the mother noticed that while the infant had developed remarkably well physically she could not hold her head up. Because the child was so chubby the mother thought she was just lazy. At six months the infant could hold her bottle. The child continued to gain but did not improve mentally. She was seen by several physicians who informed the mother that the child had a birth injury

At the age of two and a half years the child was beginning to sit alone and could hold her bottle. She weighed 35 pounds. At this time she developed an acute illness with fever and an eruption which the mother says looked very much like

measies but her doctor diagnosed as scarlet fever— She was quite ill at this time lost much weight and was very weak. She gradually recovered but it was now noticed that when the child reached for her bottle she would grope something that she had not done before. In addition it was noticed that she was wobbly? Except for this one illness the child had been well

There have been no inoculations or vaccination

On physical examination the child was seen to be obviously defective mentally She was quite chubby her height wn 35 in hes and weight 38 pounds. The tem perature was normal. The child would occasionally grimace and roll her head to one side or the other. She would roll her body and the spine was quite bowed She was unable to walk.



Fic 1

The face showed but little expression The hair showed nothing unusual and the scalp was apparently normal

The eyes showed no strabismus or nystagmus. She would follow her bottle and a light. The pupils were regular equal and reacted to light. Ophthalmoscopic examination showed a slight increase in paleness on the mass side of the optic nerve.

The teeth and gams were normal

The spine showed a kyrhoscoliosis. There was considerable weakness of the spinal nuncles

The heart and lungs were normal

The abdomen was rather flabby The spleen and liver were not palpable

The lower extremities showed a great deal of flabby tissue with poorly developed nuscles. Motion was considerably restricted. When supported, the child kept the legs together though there was no abductor sparm. There was dorsiflexion of the large toes.



Flg 2



Fig 3

The child had fair use of the arms with marked ataxia and could hold her bottle. Muscle development was only fair

The neurologic examination of the eranial nerves showed no abnormalities.

There was some weakness of the muscles of the trunk resulting in the kyphoscollosis. The child could not crant or naik and when sitting down was ataxic and would gradually roll over on her back to nurse her bottle

The biceps, triceps, patellar and unkle reflexes were hyperactive. Plantar stimu lation gave dorsification of the large toe

Sensitivity was apparently normal

The blood Wassermann was negative. Spinal puneture was not done

#### PATHOLOCY

The changes in the posterior columns are the most definite and invariable features of hereditary ataxia being essentially a systemic degeneration with neurogliar probleration of the dorsal column. The disease process is not confined to the posterior columns but is more diffused with the causation quite obscure. The tracts most commonly involved are the crossed pyramidal tracts, the columns of Goll and Burdach Gower's tract, the direct cerebellar tract, and, in some in stances, Lissauer's tract and the column of Clark. In the upper part of the cord the degeneration, as a rule, is not so pronounced but in the lumbar and sacral regions the degeneration involves almost completely the dorsal column.

A number of reported cases record no sensory disturbances This paradox of preservation of sensation with pronounced degeneration of the posterior columns has been variously explained Friedreich1 said that the dorsal columns could not be the principal sensory tracts Muller2 came to the conclusion that the sensory impulses were con ducted by naked axis evlinders within the degenerated tracts Desermes thought that sensation was not affected by degeneration in the columns of Goll and that alterations in the posterior columns may exist without sensory changes Mott' claims that the neurones con sisting of small cells and fine fibers which subserve cutaneous sensory and viscerovascular functions, are not affected in Friedreich's disease as in tabes dorsalis and in consequence there are no visceral disturb ances or loss of cutaneous sensibility Pfeiffer' believes the charac teristic sensory loss when found in Friedreich's ataxia is an essential rather than an exceptional feature in the symptomatology of the dis ease He points out that when the forms of sensibility transmitted by the dorsal columns are impaired with only moderate ataxia, the de generation affects principally the posterior tracts, but when sensory loss is slight in proportion to the ataxia the spinocerebellar tracts are affected more intensely than the dorsal column tracts

#### DISCUSSION

The causation of hereditary ataxia is obscure and has given rise to a variety of theories. The fact that it occurs in several children of

the same family at once suggests some obscure familial defect, but the additional fact that numerous brothers and sisters often escape indicates that the cause, whatever it is, is strangely limited or selective in its action Gower's theory that the disease is due to an abiotrophy, or developmental defect, has been received with some favor

Williamson<sup>6</sup> suggested that the location of the lesions in the posterolateral regions of the cord may be due to a less adequate blood supply. the supposition being that the local resistive power is less regions receive their blood supply from small meningeal branches instead of the deep central artery as in the anterior and central parts of the cord

That the disease first makes its appearance with an acute infection is well recorded. Hess' reporting case histories of twin boys developing Filedieich's ataxia after an attack of influenza in 1918 raised the question as to whether he was dealing with boys with a normal mental and physical system who had undergone an acute infection of the nervous system resulting in degeneration and scoliosis, or whether the acute infection resulted in degenerations in congenitally defective nervous systems, and came to the conclusion that he was dealing with Friedreich's ataxia Lloyd and Newcomer<sup>8</sup> 1eport two children, of the same family and of the negro race, with indications of an unstable nervous system, the younger of whom developed ataxia at the age of six when he was recovering from typhoid fever. The development of ataxia in the present patient who obviously had a poor mental pattern was immediately preceded by an acute infection

## SUMMARY

A case of hereditary ataxia of the mixed type occurring after an acute infection in a white female child of two and a half years is reported

The child in question had an obviously defective mental pattern

## CONCLUSION

Evidence is presented that given a congenitally defective nervous system in a child an acute infection can initiate a degenerative process of the dorsal columns of the spinal cord

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# VIRILISM AND HYPERTYNSION IN INCINCY ASSOCIATED WITH ADRENT PLAGE

## FRANK VI DET BEGERT MD SCHINFOTADI VI

VIRILISM associated with adread tumor has been frequently reported. Lesions of the pit utary may apparently produce a similar picture but Cushing a syndrome tattributed to pituitary baso philism does not appear to include the changes in external genitals so striking in adrenal subjects and has been more often encountered in its extreme form in young adults. In an attempt to explain the similarity of signs produced by lesions of the anterior lobe of the pituitary and the suprarenal cortex Langdon Brown<sup>2</sup> calls attention to the fact that both of these glands are in close association with nervous structures, the adrenal medulia being developed from sympathetic ganglion cells and the pituitary connected with the hypothalamus

Renal hypernephroma apparently more common in later life is not believed to produce any alteration in sexual characteristics. A small number of malignant tumors of the overver are accompanied by premature sexual development which according to Frank? must be ascribed to the influence of the overian growth because of the fact that recession of the prematurity takes place after the removal of the tumor naturally no virilism would result. Pineal tumors although they may cause sexual precosity and obesity are not known to cause virilism. They apparently occur for more frequently in boys.

The case to be reported is unfortunately incomplete in that no autopsy was permitted and therefore no opportunity to examine the head postmortem the very small sella turcica appearing in the x-ray film, however, strongly suggests the nonparticipation of the pituitary. The suprarenal factor was definitely demonstrated at operation the manifestations being those expected from a suprarenal growth occurring in infancy obesity precocious development, hirsuities voice change virilism, and marked hypertrophy of the clitoris and external genitals together with hypertension and cardiac enlargement.

The infant two years and two weeks old and of Italian parentage entered the Pediatrie Department of the Lilis Hospital on March 11 1933. She was brought in by the parents, who feared a convulsion with the history of having had convulsion on and off ever since lifth. On the day of admission she had become very

on and the ever since within the lasters of mild degrees of precedity in two related children one a couch. The father is exceptionally dark and virile in appearance the mother large, dark and handsome rather than pretty

Development was described as normal up to the end of the ninth month. She was mentally alert sat up, walked talked and cut her teeth at the usual age periods

but at nine months she began to gain weight very rapidly and a dark growth of hair was noticed all over the body

The infant was well supplied with subcutaneous fat, especially about breasts, shoulders, and face, her weight was 38½ pounds, her features were masculine, and

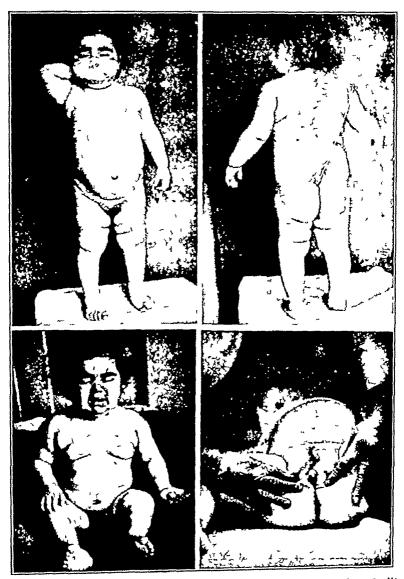


Fig 1 -General appearance of child showing growth of hair and enlarged clitoris

she had a profuse growth of black hair on the back and public region, heavy eye brows, and a rather definite mustache. The scalp hair was abnormally heavy and extended onto the face. Her dental formula was normal for her age. A papular rash and some pigmentation of skin were noted. Most striking was the development of external genitals, enormous hypertrophy of the chitoris, prominent vulvae, and a

dense growth of public hair the vaging pervious and the urethra in the normal position in relation to vaging and elitoris.

Physical examination showed the bart (vidently enlarged to the left and a mass could be felt in the right abdomen or at least a distinct difference in the two sides was evident upon percussion and pulpation although study of the abdomen was rendered exceedingly difficult by the best blood pressure registered 160/110 and the eyegrounds were reported as shown evidence of hypertension. Dr Park, who made the ophthalmoscopic studies riported tortuesity of the blood ressels similar to that found in cases of high blood pressure before learning of our pressure findings.



Fig - ray of skull showing small sells turcles.

X ray of the skull taken laterally showed nothing other than a solla turclea which appeared extremely small. This might be interpreted as indicating a small pituitary but it is only fair to note that the significance of this finding has been questioned. The thickness and contour of the cranium accmed normal for a child of that age. The heart shadow was extremely large in keeping with the blood pressure and confirming the physical findings. A more than normal openeity in the right abdomen seemed to give additional confirmation to the diagnosis of right adrenal tumor. A ragged appearance of the lower cpiphyses of the femora was demonstrated hard ness of the clinical processes has been noted in two cases quoted by Langdon Brown as apparently due to deficiency of calcium salts. Soveral examinations of the urine

revealed only a large amount of amorphous material and a very faint trace of albumin, sugar was always absent, no blood was found, the number of leucocytes in significant

Blood Wassermann and Kahn tests were negative. Blood sugar 136 mg per 100~ee, possibly somewhat high, crythrocytes and hemoglobin low, with a leuco extess of 24,000 two days before operation

The patient was operated on the eighth day in the hospit il by Dr. Stanton, and I quote from his record. Uterus apparently normal for age. Ovaries (estimated)  $1\times 4\times 3$  cm, equal in size. Both adrenals were large, the left smiller than the right which was adherent to the liver and measured approximately 9 by 6 by 7 centimeters, and so soft that it indicated malignancy, both were separate from the kidneys. The right adrenal was shelled out subcortically. Very little hemorrhage was reported at operation, although there was some coving from the incision later. Death occurred within thirty six hours.

No postmortem study was possible other than examination of the tumor mass by Dr Ellis Kellert. Its weight was reported as 79 7 gm, the specimens consist

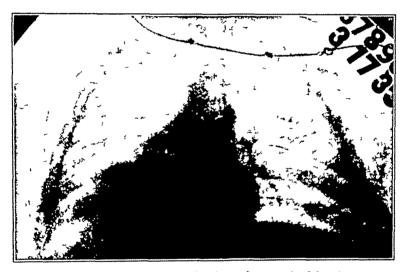


Fig 3-X ray of chest, showing enlargement of heart.

ing of several masses of prie vellow, blood stained, fatlike tissue, extremely ragged and irregular in shape, the largest piece measuring 6 by 4.5 by 3 cm. This piece, on section, was seen to consist of soft hemorrhagic tissue somewhat resembling dark red blood clot at the margins of which was soft, grayish tissue. Dr. Kellert reported that sections showed a cellular tumor together with extensive areas of necrotic tumor tissue and hemorrhage, the tumor cells large, poorly defined, and varying greatly in size. They appeared to be somewhat rounded and contained vacuolated cytoplasm. The nuclei varied greatly in size, many macronuclei and all stages of chromatic change being present. Certain cells contained several nuclei and others nuclear figures. The cells showed no definite arrangement but there was a slight tendency to grow in columns. Very little stroma was present. Anatomical diagnosis. Adrenal carcinoma

The case is of the cortical type with definite, easily interpreted syndrome, although lesions of the pituitary and pineal must be excluded as causative factors. Tumors of medullary origin of the type first

described by Hutchinson product only various symptoms referable to the abdomen until the characteristic my avenient of the skull occurs, their early diagnosis seem that by possible although Peterman, commenting upon a case of his own states that tumors of the right suprarenal gland usually produce the main liptum and thus direct attention to their presence

In a recent number of the 1n m of 8m pery Lehman of the University of Virginia writes of a cale at a lenal tumor removed from an infant of eleven months by Willard fartlett of 8t Louis. A description of this case was published in 1917 and commented upon as distinctive among undifferentiated tumors as the first case successfully operated upon. The child was alive and in perfect health fifteen years later. Collett's case operated upon in 1921 was at that time believed to be the first to recover although recovery was not complete, all signs of virilism having not yet disappeared after two years. This case is especially interesting in that an indirect larvingoscopic examination revealed the yocal cords unusually long and broad almost as in an adult male. Since years later Harris and Plewes reported theirs as the second successful case.

Probably the youngest recorded case is that of Lightwood <sup>7</sup> a male infant of eighteen weeks. The appearance of the baby was described as peculiar on account of the visible hard deposits of fat in the cheeks and around shoulders and scapulae. There was a florid color of the face and the hair on the head was plentiful with slight growth on the forchead but no development of hair elsewhere. A mass was felt in the left flank which appeared larger and lower than a normal left kidney. Pneumonia developed and death occurred eleven days after admission to the hospital. The tumor was demonstrated at autopsy

In the last few years the results of surgical removal have been most encouraging though certainly dependent in malignance upon early recognition before metastasis has occurred. Cecil's recent statistics show that all the cases that had cortical hyperplasia and adenoma excepting where congenital recovered from the operation and also were cured of the disease with loss of abnormal distribution of hair and fat and recession of the chtoris to normal. Twenty two per cent of the patients with hypernephroma completely recovered. Since most of the fatalities occurred within a few hours after operation a technic designed to prevent shock is essential. Cecil advises tying of the vessels particularly the veins before manipulating the tumor to obviate the danger of metastases of detached particles and to prevent a large amount of secretion from being suddenly squeezed into the circulation. It is imperative to know that the corresponding gland is functioning.

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## THE TREATMENT OF PEPTUSSIS WITH GOLD TRIBROMIDE

#### REPORT OF SEVENTY FIVE CASES

J LESTEIN M.D.

PERTUSSIS is one of the ommen communicable diseases of child hood affecting all races in all climates. It varies greatly in its epidemiology, virulence and seasonal prevalence. Since the disease is universal and there is only a siight natural immunity to it, the number of whooping cough cases must be very large. The death rate from whooping cough per 100,000 population in the registration area in the United States for the last thirty years averages 9.92. The younger the child, the greater the mortality. The number of children in the United States dying from pertussis and its complications is estimated to be about 25,000 a year.

History—In all probability, whooping cough was known to the early Greek Roman, and Arabian physicians and to the physicians of the middle ages. The first epidemic of pertussis occurred in Paris in 1578 and was described by Ballonius. The second epidemic occurred in London in 1658 and was recorded by Thomas Willis. Sydenliam described the disease more fully in 1670 and again in 1679. Pertussis appeared in Germany in epidemic form in 1724. During a general epidemic which spread throughout Europe in 1732, the disease was carried to America.

Etiology—An organism of the influenza group which is known as the Bacillus pertussis or the Bordet Gengon bacillus has been generally accepted as the etiologic agent of whooping cough. A great deal of doubt has recently been east on the etiologic relationship of this or ganism to pertussis. Much research work is in progress on the etiology of whooping cough and some filtrable virus may be found to be the real cause of this universal disease.

Anatomic and Physiologic Pathology—The chief anatomic pathologic condition in pertussis is a catarrhal inflammation of the upper respiratory tract with degeneration of the chiated epithelium. The mucous membrane secretes a thick, whitish, tenacious substance consisting chiefly of mucus epithelial cells, lencocytes, and microorganisms. The submucosa is swollen and edematous and there is in many cases, a peribronchitis with a peribronchiclistis. There may be other pathologic conditions affecting various organs as a result of the toxemia or the physical violence due to the stress and strain of coughing. The physiologic pathology is characterized by a hyperirritability of the cough center. The toxemia of whooping cough lowers the threshold of the cough

center so that the slightest central or peripheral irritation causes a shower of coughing spasms. The proximity of the coughing center to the respiratory and the vomiting centers accounts for the respiratory distress and the frequent vomiting in pertussis.

Diagnosis —In the majority of cases, there is no difficulty in making a correct elimical diagnosis of pertussis. A bacteriologic, hematologic, or serologic diagnosis is of value in doubtful cases. A history of exposure to the disease a persistent paroxysmal cough with a tendency to be worse at night, a negative finding on physical examination, and an apparently well child between the paroxysms are indicative of whooping cough

#### TREATMENT

During the middle ages, and even up to the seventeenth century, whocping cough was treated with inational folk-remedies. Later various herbs were highly recommended. At the present time, a large number of drugs are being used with poor therapeutic results. Vac cines have been used for some years with gradually diminishing enthusiasm. Convalescent blood serum has been tried and discarded Ether, given intramuscularly or by rectum, has been in voque for some time, but has proved of little value and much discomfort. X-ray treatments over the chests of whooping cough patients have been tried but have not gained much therapeutic popularity. Carbon dioxide inhalation was recently suggested but its practical application is difficult in general everyday practice.

In an effort to find some reliable medicine for the treatment of pertussis, I began several years ago the study of the therapeutic effect of the anti-whooping cough drugs in common use. I divided them as nearly as possible, into hypnotics, sedatives, and antispasmodics and gave each group a careful and thorough trial in a fairly large number The results were not encomaging. I then made a special study of the bromides and classified them into monobromides or univalents, dibiomides or bivalents, and tribiomides or trivalents tassium bromide (KBi), sodium biomide (NaBi), lithium bromide (LiB1), and ammonium biomide (NH4B1) are univalent biomides Calcium biomide (CaBi2) and stiontium bromide (SiBi2) are bivalent bromides Gold bromide (AuBi3), non bromide (FeBi3 or Fe2Bi6) arsenic biomide (AsBr<sub>3</sub>), and aluminum biomide (AlBr<sub>3</sub>) are trivalent In observing the action of the biomides, I found that the dibromides gave better sedative or bromine action than the monobromides and the tubiomides were more effective than the monobromides or the dibromides Of the tribromides, the most suitable preparation for medicinal purposes is gold tribiomide. This drug I have used in whooping cough for the last four years with satisfactors results

In the therapeutic study of gold in whooping cough I used the neutral salt of gold tribromid. This is a compound of gold and by drobromic acid which has no free acid. It is brownish black in color deliquescent and soluble in water. Its gold content is about 45 per cent. This chemical is to be distinguished from acid bromauric N. F. which is an acid salt of gold and hydrobromic acid with some free acid. It is reddish brown unstable, very deliquescent, and freely soluble in water. It contains about 32 per cent of gold.

The pharmacologic action and the therapeutic effect of gold tribrounde in pertussis is probably due to a specific chemical reaction between the gold and the tribromine ions with the formation of a compound which has neurosedative, antispasmodic and antibacterial action. The compound of gold tribrounde reduces the reflex irritability of the cough center and causes general sedative and antispasmodic effect. It shortens the period of the illness diminishes the number and severity of the paroxysms, and prevents complications

Treatment consisted in the administration by mouth of a solution of gold tribronide in water. The dosage varied with the age of the child and the severity of the paroxysmal cough. As a general rule ½0 to ½0 of a grain three times a day after meals and once at mid night was given. It was found however that a solution of gold tribronide in water did not keep well on standing for some time. There were frequently some slight chemical changes with a sedimentation due probably to oxidation. To avoid using an unstable medication I am now prescribing a uniform stable palpable preparation known as Elixir gold tribronide (Flixir bromaurate). The dosage is a teal spoonful three or four times a day after meals.

Result of Treatment —The result of treatment in 75 whooping cough cases during the last four years was most encouraging. Of the 75 patients, there were 43 females and 32 males the ages ranging from two weeks to eight years. There were 2 adult cases. In about two thirds of the whooping cough patients the cough subsided in three weeks, in the others it abated within from five to seven weeks. In all cases after three or four days treatment with gold tribromide the cough was less frequent and less distressing the attacks were shorter and milder the vomiting ceased and the sleep was more restful. There were no recurrences, complications or fatalities in this series of cases. In 25 controls who received the usual antipertussis remedies the cough was frequent and racking and the course of the disease was long varying from three to four months.

Postural Treatment—It is well known that the cough in pertussis is worse at night. In fact, this has been accepted as one of the symptoms of pertussis. The reason for the incessant coughing at night has

Elixir Gold Tribromid (Flixir Bron curate) may be obtained from Schieffelin &

never been made clear. It occurred to me that this was due to an overstimulation, during sleep, of the cough center which is hypersensitive in pertussis. In the recumbent, sleeping position, the lungs do not expand fully and there is a decrease in oxygen and an increase in the carbon dioxide of the blood. This increased concentration of the carbon dioxide in the blood causes an over-activity of the hyperiritable cough center giving rise to the distressing paroxysms at night. To overcome this most annoying condition, I have whooping cough children sleep in a semi-reclining position. When propped up in bed, there is a better ventilation of the lungs with free respiration, more oxygen inhalation, less carbon dioxide concentration and less stimulation of the cough center. This simple postural treatment is giving whooping cough children considerable rest at night

## SUMMARY

Whooping cough is a serious disease in its mortality rate, complications, and sequelae. It affects all races in all climates. It is essentially a disease of childhood. The etiology of pertussis is still not definitely established. The anatomic pathology shows an inflammation and degeneration of the upper respiratory tract. Physiologically, there is a hyperintability of the coughing reflex are which responds to the slightest physical or psychic stimuli. Most of the treatments recommended for whooping cough are either ineffectual or not practical of application. As a result of a study of many drugs, especially the bromides, in the treatment of whooping cough, gold tribromide is seemingly an effective remedy in a large number of cases. The earlier in the disease the treatment is begun, the quicker and better the results. The compound of gold tribromide inhibits the coughing reflex are, allays the general nervous irritability and relieves the spasmodic attacks which cause damage to every system of the body.

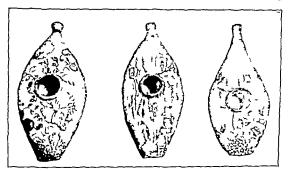
222 EAST EIGHTY SECOND STREET

## ANTIQUES OF PEDIATRIC INTEREST

## T G H DRAKE, WB FRCP (C)

 ${f A}^{
m S}$  EARLY as 1686 pottery works had been established in Stafford shire where clay and coal were easily obtainable

Josiah Spode the founder of the Spode firm was originally apprenticed to Thomas Whieldon, where he worked with Josiah Wedgwood In 1770, he bought the potters works of Banks and Turner at Stoke and in 1797 was succeeded by Josiah the second during whose period William Copeland was taken into the firm Josiah the third died in 1829 In 1833 Thomas Garrett joined the firm and until his retirement in 1847 the firm was known as Copeland and Garrett late Spode.



Spode Stanfordshire transfer printed pottery feeding bottles (length 7 inches)

Marks Left and right, Copeland and Garrett late Spode, circa 1833 center
Copeland late Spode circa 1847

Since that time the style has been Copeland late Spode. The many productions associated with this famous factory are still perpetuated by Messrs W T Copeland and Sons.

In 1780, Thomas Minton engraved his famous willow pattern evolving and arranging his design from several different Chinese sources. Originally there were only two figures on the bridge, no flying doves and no conventionalized cedar. The pattern was an immediate success different versions were engraved with additions from other Chinese originals and finally the pattern as we now know it was evolved. From the final composition has grown up the legend of

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the love of a daughter of a Chinese mandarin for her tather's secretary and the punishment by imprisonment of the daughter by her father who had intended her for an old but wealthy surfor, of the escape of the lovers to the cottage by the sea where the life honeymoon was to be spent, the burning of the cottage by the disappointed outer and the transformation of the lovers by the Immortal Gods into two doves

Transfer printing of pottery was introduced into Staffordshire by Josiah Spede in 1784 with the old willow pattern. Later other blue printed designs were used

Transfer printing is a method of printing on a rigid or uneven surface by means of paper prints applied to the ware. It was probably used first by the Battersea Enamel Works about 1750. Some what later its use in decorating pottery was discovered independently by Sadler of Liverpool who with Green was so successful in this method of decoration that pottery was sent to them from all parts of the country for printing

In transfer printing a metal plate, usually copper, is engraved in the usual way but somewhat deeper than for printing on paper since the firing of the pottery reduces the strength of the colors. The color is then rubbed into the lines of the warmed plate the superfluous pigment is scraped off and the surface is wiped clean with a pad. A print is taken on damped tissue paper and this is applied to the ware and carefully rubbed into contact. The piece is next immersed in water, which removes the paper and leaves the print unharmed since the pigment is mixed with linseed oil. The piece is then fired over or underglazed as the case may be

## Critical Review

### TUBERCI LOSIS IN CHILDREN

LEC FORREST HILL MD DIN MOINER IOWA

THE Critical Review of the October 1932 issue of The Journal of Pediatrics, the attempt was made to sum up the prevailing views on tuberculous in children. This discussion is intended as a continuation of that report and is based on the literature of the past year

The National Tuberculosis Association' has published a second brochure entitled Childhood Tupe of Tuberculosis Diagnostic Ands, with chapters by Opie Aronson Mel hedran, and Chadwick. It has received the approval of the committee on Childhood Tuberculosis of the American Sanatorium Association and is to be highly recommended to those who wish a clear and concise presentation of the subject in condensed form

Dr J A Myers has also published a second bool called The Child and the Tuberculous Problem which not only sums up in detail the present conceptions of the subject but also contains many advanced ideas which he has acquired as a result of his extenive stadies at

Lymanhurst during the past decade

The set up at Lymanhurst has embodied an unusual opportunity for a follow up study of a large number of inberculous children over a period of ten years. The results of this ten year period of study have been published by Dr Wyers, chuf of staff and by Dr Chester Stewart pediatrician on the staff in a number of articles. Their observations have forced them to conclusions that in many instances are in direct conflict with beliefs generally held but which on the whole have tended to simplify and clarify the whole picture. In the pages that follow the opinious of these authors have been freely set for the purpose of bringing out fully these new concepts established by them

#### TERMINOLOGY AND CLASSIFICATION

Some controvery exists in the literature as to the classification of the various types of lesions occurring in children as the result of first infection by the tubercle bacillus. The brochure referred to above states that. The childhood type of tuberculosis is the name adopted by the National Tuberculosis. Association to describe the diffuse or circumscribed lesions in the lungs and associated tracheobronchial lymph nodes resulting from a first infection of the pulmonary tissue with the tubercle bacillus. It is recommended that this term childhood type of tuberculosis, be used instead of infantle 'juvenile' or hilum tuberculosis. It specifically included lesions of the tracheobronchial lymph nodes. The childhood type of tuberculosis is usually found in children. It infrequently occurs in white adults but is not uncommon in adult negroes. Mexicans. American Indians, Lorto Ricaus and Filipinos."

In a subsequent chapter McPhedran classifies the lesions of child-hood type tuberculosis on the basis of x-ray observations as follows "A Focal tuberculosis, caseous or calcied nodule B Tuberculous consolidation of a lobe or wedge, progressive or unstable, calcified spots remain if it clears C Tuberculous consolidation of a lobe or wedge, retrogressive and benign Few strands remain when it clears D Diffuse, childhood type tuberculous infiltration Confluent bronchopneumonia is the serious lesion of this type and often precedes E E Miliary tuberculosis F Tuberculosis of tracheobronchial lymph nodes, uncalcified G Tuberculosis of tracheobronchial lymph nodes, calcified"

Myers3 states that their present classification consists of

- 1 Negative to tuberculosis In this group are placed those children who are negative to the tuberculin test when a full milligram of tuberculin has been administered intracutaneously, and who have no other abnormal findings due to tuberculosis
- 2 Primary tuberculous infection This group consists of those children who react positively to the tuberculin test but in whom no evidence of tuberculous disease can be obtained by x-ray, physical, or laboratory examinations
- 3 Childhood type of tuberculosis. In this group the children react positively to the tuberculin test and in addition have some evidence, usually by x-ray, of the location of the focus or the foci. The lesion may be represented by a shadow indicating an inflammatory process which is progressing, stationary, or receding, or it may be represented by shadows indicating deposits of calcium. These lesions need not necessarily be in the chest. When evidence of calcium deposits is found in lymph nodes anywhere, particularly in the cervical region or in the mesentery, the classification is that of childhood or first infection type of tuberculosis. Further subdivided into
- (a) Those with the inflammatory stage when first seen, progressing, stationary or receding
- (b) Consists of those lesions in which deposits of calcium can be demonstrated by x-ray examination
- 4 Adult type of tuberculosis In this group have been placed all of the definite clinical forms of tuberculosis whether the lesions appear in the lungs, bony framework, or elsewhere

Myers expresses dissatisfaction with his second group. He feels that a sharp line should not divide cases with demonstrable lesions from those without demonstrable lesions when a positive tuberculin test is present in both groups. He believes it is erroneous to attempt to distinguish between tuberculous infection and tuberculous disease. A positive tuberculin test means a focus of tuberculous disease somewhere within the body, and only the pathologist has the right to say whether it is "healed" or not

Stewart in a more recent article expresses his belief that the terminology and classification set forth in the previously mentioned brochure should be revised in order that it be more in keeping with the known facts concerning first infection with the tubercle bacillus. The term "childhood type tuberculosis" as now defined limits itself to include lesions occurring only in the lungs and tracheobronchial lymph nodes. Since the primary focus or foci of infection may be extrapulmonary, and since the childhood type of tuberculosis does occur

in adults, Stewart feels that the terms "first infection types of tuber culosis" or "primary tuberculosis" would be more appropriate. Fur thermore he objects to the term, adult tuberculosis, on the basis that this lesion does occur in children with appreciable frequency. He prefers that these lesions be designated by the term, reinfection type of pulmonary tuberculosis.

Ho is not satisfied with a classification based upon appearance of lesions in the x-ray films of chests. Compared to the tuberculin test and pathologic examination the x-ray is a relatively crude screen since in only about 25 per cent of first infection cases does the x-ray reveal lesions with sufficient clearness to be identified as such. Ghon's in his well-known pathologic studies was able to demonstrate a tuber culous focus in 90 to 95 per cent of positive tuberculin reactors. Both Stewart and Micris express their conviction that a positive tuber culin test specifically indicates a tuberculous focus somewhere within the body, but our present methods of examination during life are inadequate to demonstrate such focu in at least half the children

Stewart further states that no evidence is found in the follow up observations made during the past decade at Lymanhurst to indicate that cases presenting single or multiple large, partially or heavily calcified scars show a definitely greater tendency to manifest symptoms of impairment in health referable to primary tuberculosis or to suffer a different ultimate fate than do infected children who have small or no lesions demonstrable during life. As far as I have been able to ascertain, all cases of primary tuberculosis are basically identical except that a few cases (from 3 to 4 per cent of infected children) with acute diffuse primary tuberculous pulmonary infiltrations exhibit symptoms which on this basis temporarily distinguish them for a time from the general group of infected cases. After these acute manifestations subside patients with first infection types of tubercu losis are clinically indistinguishable from one another as a rule and remain so until the day arrives when reinfections transfer a certain percentage of them to the consumptive group?"

A classification proposed by Stewart outlines roughly the stages of evolution of tuberculosis as it occurs in man. The first group consti tutes the general population A second uninfected group is identified by negative tuberculin reactions The third group is the primary tuberculosis group or first infection types of tuberculosis or 'patients whose bodies harbor foer of tuberculosis of first infection (identified by positive tuberculin reaction) [This group includes first infection pulmonary (childhood type by definition in the brochures) retroperatoneal or cervical lymph node tuberculosis)] Note may be made in these cases relative to the appearance of lesions found but assumptions that visualized conditions provide reliable evidence that these cases differ basically and require grouping separate from others in the general first infection group apparently are unwarranted' The fourth group contains first infection types of tuberculosis with symptoms Only 3 or 4 per cent of infected children are in this group and their sojourn here is temporary. The fifth group is comprised of first infection types of tuberculosis without symptoms definitely refer able to their disease The majority of cases fall in this group The sixth group is designated as the secondary tuberculosis group or first infection types that later develop reinfection types of tuberculous (consumption, and the like) The final group is the primary tubercu

losis group or first infection types of tuberculosis that do not develop reinfection types of tuberculosis

Washburn<sup>6</sup> feels that on the basis of newer knowledge secured by tuberculin, x-ray, and pathologic studies the terms the "pretuberculous" or "potentially" tuberculous child, "latent" or "suspected" tuberculosis are of doubtful value as diagnoses. The attempt to distinguish between "tuberculous infection" and tuberculosis he thinks is also of dubious significance, and the term "tuberculosis of childhood type" may be misleading. He prefers the classification as proposed by Ranke" in 1916 in which the disease process is divided into three stages, a primary phase of invasion, a secondary phase of spread to lymph nodes associated with the development of an allergic response, and a tertiary phase which represents actual visceral involvement. The first two stages commonly occur in childhood and the third in adult life, but all three may be found in infancy. This is essentially the view of the German School as set forth in the Handbuch der Kindertuberkulose for 1930 by Herbert Koch, Epstein Engle Priesel Zarff Liebermeister, Weise, and others as referred to by Collis and Brookington s

Blau and Rosenbaumo feel it is a misnomer to designate the primary complex of Ranke as childhood tuberculosis. This latter term "should be limited to eases in which a definite and distinct parenchymatous involvement is depicted by the xiax, with a positive Mantoux test, and with more or less distinct clinical manifestations, simulating in a measure pulmonary tuberculosis in the adult." They feel the pulmonary tracheobronchial gland lessons defined in the brochure as child hood type tuberculosis should be designated by the term "primary pulmonary tuberculous complex."

It is apparent, therefore, that there is still lacking by a wide margin a uniform opinion in the interpretation, terminology and classification of lesions produced in the human body by the initial infection with tubercle bacilli

## LESIONS

From studies such as those which have been carried on at Lyman huist and elsewhere, sufficient data have been collected to give the physician some idea of what he may expect in the way of x-ray findings in his positive tuberculin reacting children. Roughly speaking at least half of the positive reactors will have negative films 25 per cent will show questionable or doubtful lesions, and the remaining 25 per cent will show definite lesions characteristic of the childhood type of tuberculosis

In the 50 or more per cent of positive reactors who give negative roentgenologic findings the primary focus may be assumed to be extrapulmonary, too small to cast a shadow, or obscured by other structures. Except for this difference of visualization, or failure of visualization of lesions it probably should be emphasized that symptomies positive reacting children are in all essential respects to be regarded alike so far as their tuberculous experience is concerned

In the 25 per cent of films revealing definite lesions, it may be expected that the parenchymal lesions will be found more often in infancy and early childhood the calcifications in middle and late childhood, and the adult type of tuberculosis in the teen age

Myers' reports his x ray findings in 4737 positive tuberculin reactors as follows. Questionable calcification in hilum 412 per cent slight moderate, and marked calcification in hilum 935 per cent, Ghon tubercles 604 per cent questionable (thon tubercles 08 per cent, calcification hilum fibrosis extending into lung parenchyma 0.55 per cent childhood type tuberculosis in lung parenchyma (inflam matory stage), 087 per cent marked enlargement hilum, without calcification 0.38 per cent marked enlargement hilum infiltration extending to parenchyma 0.8 per cent it ctal positive findings 22.91 per cent adult type tuberculosis 1.28 per cent

Stewart<sup>10</sup> in a group of 579 positive reactor, found the following lesions revealed by the x-ray Resolving parenchymal [comparable to childhood type tuberculosis in lung parenchyma (inflammatory stage) of Myers], 47 per cent questi mable elefication 86 per cent slight calcification 138 per cent mod rate calcification 52 per cent modrate calcification, 22 per cent down tubercles, 116 per cent adult

type tuberculosis 22 per cent

#### REPORTED TO A TO A LESIONS

Some further discussion of the lesion referred to above by Myers as the childhood type tuberculosis in lung parenchyma (inflammatory stage), and by Stewart as resolving parenchymal pulmonary tuberou losis seems warranted. It is probable that this is the same lesion referred to by Ehasberg and \culand, Goldberg and Gasul and oth ers, as "epituberculosis" and in all probability in the past the terms splenopueumonia ' 'gelatinous pneumonia ' perifocal inflamma tion " circumfocal inflammation paratuberculosis lous inflammation,' and ' collateral inflammatory edema were all used to designate this same type of lesion. In common with all descriptions, has been the basic fact of a more or less massive slowly resolving pulmo nary shadow, characterized by pancity of physical signs and symptoms oc curring in children who have positive tuberculin reactions. According to Stewart 10 such lesions represent the earliest stage of the primary pulmonary infection. Up to date he has observed seventy three such Two of these have been under observation for nine months a third for twenty eight months and the remaining sixty eight cases for periods ranging from three to nine years. No deaths have occurred He states that 'In most cases (all in our experience) extensive paren chymal lesions resolve and disappear leaving relatively inconspicuous calcified sears and, during the months this resolution is taking place the patient, whether a young infant or an older child may enjoy excel lent health At times severe and alarming symptoms are present for variable periods early in the course of the disease following which a long period of symptomless convalescence ensues '

Martinii in California presents a series of sixty cases that she has seen. She divides them into three groups on the basis of variation in physical signs and symptoms rather than on any fundamental pathologic differences. All the children had positive tuberculin tests. Sixty five per cent had a history of contact. Eighty per cent of the children were under six years of age. All had pulmonary infiltrations of varying degrees of massiveness as revealed by the x-ray. Twenty nine were acutely ill with physical signs of consolidation. Eighteen of the sixty were alling but had slight or absent physical findings. Thirteen were apparently healthy children with practically negative symptoms.

and physical findings Four of the series died. Three of these were in the acutely ill group and were seriously ill when first seen, the other death, due to tuberculous meningitis, was in the second group. In the remainder, the parenchymal lesion gradually resolved leaving either an area of calcification or cleared completely. At electasis of a lobe was present in three cases. Evidence of enlarged tracheobronchial lymph nodes in association with the pulmonary infiltrations was present in 45 per cent of the series. Martin does not feel the presence of these enlarged glands added greatly to the gravity of the prognosis. She concludes that "acute tuberculous pneumonias are more frequent than is generally recognized. They have a good prognosis if seen early, and if repeated infection is prevented by separation of the child from the source of infection."

Bruce<sup>12</sup> also discusses this lesion and the favorable prognosis of primary tuberculosis in general, and presents films of four cases of pulmonary tuberculosis which he has seen undergo satisfactory resolution

Reichle,13 in a most interesting article, discusses the mechanism of resolving exudates in tuberculous children He regards the observations of the authors who first called attention to these massive lobar shadows as being of crucial importance However, he believes that up to the present time there is no unanimity of opinion concerning the nature of such lesions Atelectasis, secondary pyogenic infection in tuberculous tissue, and lymphatic congestion have been suggested as mechanisms The majority, however, look upon these exudates as being areas of inflammation about tuberculous tissue, the inflammation being due to a "poison" from the destroyed tissue or a "toxin from the tubercle bacillus in the focus of 'true' tuberculous inflammation '' The rôle played by allergy in the production of these resolving or "fugitive" exudates is discussed by the author. He states that "allergy is probably an essential condition of a fugitive exudate". To quote further, "The primary intection occurs in virgin soil, the tissue is not specifically sensitized to the tubercle bacillus and its chemical constitu-This is probably the reason for the minuteness of the lesion, the slight surrounding inflammation, and the ultimate state of characteristic morphology Never again can the body react to the tubercle bacillus in this fashion, every subsequent defense will be conducted with a striking increase in the auxiliary phenomena of peripheral vascular dilation and extravasation of the cellular and amorphous material which constitutes an inflammatory exudate The second characteristic of hypersensitive tissue is its tendency to undergo the type of necrosis known as caseation" He feels that the majority of the lesions under discussion are tuberculous pneumonias which have failed to go on to caseation, some may be atelectases, and some lobar or bronchopneumonias. He disagrees with Stewart's idea that these iesolving lesions are restricted to the stage of the primary infection He concludes that "since resolution is possible in almost every form of tuberculous inflammation, there is no reason for calling on any unusual mechanism to explain the retrogressive tuberculous exudates "

H C Cameron<sup>14</sup> describes a case of apparent resolving parenchymal tuberculosis which cleared rapidly leaving a small focus. He concludes "that the existence of benign infiltration remains to be proved. It can only be demonstrated by the accident of an opportunity being afforded to perform an autopsy during the time when the extensive consolidates."

consolidation is present "

Whether the lesion which has been referred to by such a galaxy of terms has some unusual pathogenesis uncommon in tuberculosis knowl edge, or whether, as Stewart suggests, it merely represents the usual course of events in primary infections is probably still an open question. However, the increasing frequency with which resolving lesions are being reported coincident with the increasing use of tuberculin and x ray suggests that in the past they have gone unrecognized, and to this extent lend support to Stewart's idea.

#### DIMUNITY

Perhaps one of the most revolutionary ideas that has developed as a result of the study of tuberculosis in large numbers of children by means of tuberculin and x ray is that a primary infection does not confer protection against phthisis. In other words, a positive tuberculin test in a child can no longer be held to be an advantage, as an indicator of immunity. Nor can it be held to be a liability to reach adult age with a negative test. Myers' has observed nurses on tuberculosis wards, who, at the beginning of their services reacted negatively to tuberculin but who later developed positive tests. X ray pictures of their chests have shown lesions similar to the primary type of infection seen in children. In no in stance has he seen 'galloping consumption' occur in adults who had grown up with a negative test as was once supposed to be the fate in store for such unfortunates if they chanced to acquire tuberculosis

If our former ideas are correct one would not expect to see adult type tuberculosis developing in healthy children with positive tuberculin tests showing evidences of primary tuberculosis only Stewart. 4 how ever, in reporting his observations on 10 000 children at Lymanhurst in the last ten years found eighty four cases of phthisis, thirty six of whom had had primary tuberculosis exclusively for varying periods up to ten years and then developed the reinfection type of pulmonary tuberculosis Twenty five of the eighty four children had primary and reinfection pulmonary tuberculosis coexisting when first examined Thus sixty one or 73 per cent of these eighty four children with phthisis presented unmistakable evidence that their pri mary infections did not prevent them from developing the serious and fatal form of adult or reinfection type tuberculosis Insufficient data were available on the remaining twenty three children to provide evi dence for or against the question under discussion autopsy table found lesions of primary tuberculosis in all cases of reinfection type or adult type of tuberculosis It would seem, there fore, on the basis of such evidence as presented above that the allergic state does not imply protection, and the necessity of preventing con tinued exposure to tubercle bacilli whether it be the infant with his primary infection just beginning, or the older child with his calcuft cation well established far overshadows all other considerations com bined in the treatment and prevention of tuberculosis in children

#### PROGNOSIS

The opportunity of watching a comparatively large number of primary pulmonary infiltrations resolve and finally end in the production of Goin tubercles or other calcifications has led Stewart<sup>18</sup> to the belief that infants and children seldom, if ever, succamb to a single primary infection. He believes an individual can resolve a primary infection

to the calcified stage once and only once. In no instance has he observed a subsequent repetition of this process in the same child, nor has he observed a case of phthisis which has developed as a direct result of a first infection Repeated reinfections may, of course, over come the natural powers of resistance of the child and result in fatal generalized or reinfection types of tuberculosis. In the days before the use of tuberculm and serial x-ray films, it was only cases of this latter type that were recognized and the natural assumption was that tuberculosis in early life was an extremely serious disease such an outcome, however is the exception rather than the rule, and that children are endowed to cope with reasonable doses of tubercle bacilli on the whole equally well, if not better than adults, is one of the remarkable changes in thought being brought about by these newer methods of study The almost universal good health found in the group of children with primary infections, the majority of whom are unaware of their tuberculosis, or when it started, has led to the logical conclusion that first infection type of tuberculosis is a benign form of the disease, in contrast to reinfection types which are progressive and tend to be fatal

#### TREATMENT

Both Myers<sup>8</sup> and Stewart<sup>16</sup> have pointed out the conclusions they have leached in regard to the treatment of primary tuberculosis. The one essential is that opportunity for reinfections must be prevented. For this reason, and because of the uniformly favorable outlook in this type of the disease, they believe sanatorium care, even with massive resolving pulmonary lesions, is undesirable and unnecessary. Well managed homes, or foster homes free from tuberculosis, provide all that is necessary in the treatment of such patients without adding the risk of reinfection, which is a possibility in the hospital ward or sanatorium.

Children who develop the adult type of tuberculosis need sanatorium care. Myers' agrees with Chadwick that collapse therapy for these cases is indicated much more frequently than has been the custom in the past.

#### EVOLUTION OF TUBERCULOSIS

By way of summary of what has been said heretofore, the following outline, representing Stewart's conception of the evolution of tuberculosis in the human lung, is presented

1 Primary tuberculous infections of the lungs are revealed by the roentgen ray films as parenchymal infiltrations, calcified glands, and Ghon tubercles

2 These lesions, although varied in appearance, merely represent different stages in the development of one and the same clinical condition, namely, primary tuberculosis, or tuberculosis of the childhood type

3 The general tendency for lesions resulting from an initial infection by the tubercle bacillus is first to resolve and later to calcify

4 The human body can resolve a tuberculous infection into what is known as the primary complex only once

5 When once reduced to calcified scars, these primary tuberculous lesions do not become reactivated later in the production of the adult type of tuberculosis (consumption)

- 6 Death seldom and possibly never results from a single primary pulmonary tuberculous infection. The prognosis is excellent in in fancy as well as in later childhood, provided reinfection is prevented.
- 7 Primary tuberculous infections of the lung if extensive produce symptoms of varying severity which subside in the course of a few to several weeks. Thereafter throughout the remainder of the life of the patient these primary lesions produce no clinical symptoms. (Occasionally a very large Ghon tubercle acting as a foreign body may crode a blood vessel and cause hemotysis and in rare instances may be expelled from the lung in coughing.)
- 8 Consumption (phthisis) does not develop as a result of an initial infection by the tubercle bacillus. The first infection occurring at any age in life uniformly resolves and calcifles
- 9 Consumption develops following a reinfection of individuals who previously have had a primary infection
- 10 The reinfections responsible for the development of phthisis are probably exogenous in origin in the majority of cases
- 11 The lesions of reinfection (adult type of tuberculosis or phthisis) usually appear in the subspical portions of the lungs
- 12 These lesions may be present for months and years without producing symptoms physical findings or showing any tendency to spread
- 13 During the teens previously dormant lesions characteristic of the adult type of tuberculosis frequently tend to spread produce cavities and cause death
  - 14 The adult type of tuberculosis seldom calcifies
- 15 Puberty seems to favor the breaking down of previously existing apparently quiescent subapical infiltrations of the adult type of tuberculosis. Primary infections occurring during puberty however behave much the same as similar infections taking place in infancy and early childhood.
- 16 Lesions of the adult type of tuberculosis tend to spread and cavitate whereas infiltrations resulting from initial tuberculous infections tend to recede and calcify
- 17 The prognosis is grave for the adult type of tuberculosis. This type of the disease frequently results in death, whereas primary infections are soldom fatal.
- 18 The relationship existing between the childhood and the adult type of tuberoulosis seems to consist largely in the tendency for the primary infection to prepare the patient for the development of phthisis should be perchance later experience a reinfection of sufficient severity to produce an intrapulmonary lesion
- 19 Phthins apparently does not ordinarily result from a lighting up of an old infection received in childhood
- 20 The part the former childhood infection seems to play in favoring the later development of phthisis depends more upon the changes which this primary infection caused with respect to the manner in which the body reacts thereafter to the tubercle bacillus and its products rather than upon a lighting up of the old disease acquired during childhood

#### MODERN CASE FINDING

One of the most important recent developments in the public health phase of tuberculosis work is area testing, or case finding. The object is to search out the spreaders of tubercle bacilli and find infected children before they have developed serious tuberculous disease. Proper disposition of these two groups is, of course, the final goal

The success achieved by the veterinalians in stamping out the disease among cattle is an example and a challenge to the workers among human beings "In certain parts of the United States," says Stewart," "certified areas exist in which no cow is in danger of contracting tuberculosis from other members of the herd, and in these certified districts to be a calf is safer than to be a baby, in so far as tuberculous infection is concerned" And again Myers<sup>2</sup> remarks that some herds of cattle are in greater danger from human sources of tuberculous infection than from bovine sources

So long as the opinion was held that tuberculosis was practically universal after the age of ten, tuberculin testing had a very limited field of usefulness, but when area testing of children showed a variation of positive reactors from 10 per cent in some rural communities, to as high as 75 per cent in certain sections of large cities, with an average among large groups of children of around 28 per cent, the possibilities of a tremendously increased field of usefulness of diagnostic tuberculin in screening out the infected from the uninfected became apparent

The x-1ay, too, must be given its full shale of credit for the new vista which has opened up in the control of the great "white plague" An x-ray film of every positive reactor is now considered an essential Amberson, Barnard, and Loew conducted an experiment with paper films and conclude that while they are not quite as clear as celluloid films, they are satisfactory for most diagnostic work, and that the disadvantage is offset by the greatly increased number of films that may be taken with no increase in expense

Also, the clearer realization that as a contagious disease, tuberculosis presents an epidemiologic problem not dissimilar in many respects to that of typhoid fever or diphtheria, has brought out the possibilities of public health regulations for the control of this disease that may in time be equally effective with those in force for the control of other contagious diseases. It is interesting to note that Geer has instituted a medical aseptic technic in the tuberculosis division of the Ancker Hospital in St. Paul. From 1928-1930 an incidence of tuberculous disease of 5.5 per cent developed among the nurses of the training school. From 1931, when the new technic went into effect, up to the present time, the incidence of tuberculous disease has been only 1.6 per cent, which compares favorably with that found among the nurses of five other general hospitals.

How long it will take for area testing of children to become as general over the country as testing of cattle now is can only be surmised. Already many states have begun in earnest to attack the problem. Massachusetts with its ten-year program, and 100,000 children tested in the first five years, is the outstanding example. Tennessee, as reported by Bishop and Stewart, of five years ago embarked on a state wide program for control of tuberculosis with "the central and dominating idea behind this program to bring about finding of every case of tuberculosis as early as possible and placing all

cases found under adequate medical and nursing care " They conclude that 'The logical means of approach in the control of tubercu losis in Tennessee, in the light of information now at hand, would seem to center around the breaking of the chain of long-continued contact between patients with fibroid and other types of tuberculosis with their household associates Eventually this would mean the establishment of hospitals or retrents for the care of the patient who is spreading tuberculous infection among members of the family and friends"

In Minnesota, Anderson" reports the results of tuberculm testing surveys carried on by ten county tuberculosis sanatoria. These ten in stitutions tested a total of 23 424 children of whom 16 76 per cent were positive, 89 16 per cent of the positive reactors were x rayed, 10 per cent showed evidence of childhood tuberculosis and 2 per cent adult tuberculosis. "The goal of these sanatoria," says Anderson, "is year by year to come closer to an accredited group of school children."

Survevs have been corried on in Delaware by Phillips, and by Sargent, in Texas by Gray and by Sellers in Colorado by Einhorn, and in Yonkers New York by Littell and Brachman, gives the results of case finding in three ligh schools in Detroit. He says that "The Detroit Tuberculosis Society a custom, of giving health certificates to high school graduates on physical examination, will in the future include tuberculin testing and x raying of the reactors."

Leggett and Myers<sup>29</sup> studied the incidence of tuberculous infection among the high school students of Morrison County, Minn Three hundred seventy six tests were made with 149 per cent positive re

actions

Hewitt and Cutts<sup>20</sup> tested 1328 high school students in Rochester, Minn, and found 115 per cent reacting positively Of thirty four students definitely known to have been exposed to open tuberculosis 618 per cent were positive 151 per cent of the positive reactors had

a ray lesions suggestive of tuberculous infection

Soper and Wilson<sup>31</sup> made stereoscopic films of all the entering classes (1644 entrants) at Yale University in 1930 and found thirty, or 18 per cent, showed evidence of pulmonary tuberculosis and 229 or 144 per cent, showed calcifications designating the childhood type In 1931 tuberculin tests were made on the 1502 entrants, 597 per cent gave a positive reaction. The reactors were examined under the fluoroscope and any showing a suspicious shadow were x rayed. Thirteen were found to have pulmonary tuberculosis. From this study the authors conclude that fluoroscopy as a method is not sufficiently accurate. The method to be used in 1932 will be a single film of all entering students. They point out the superiority of routine roentgen ography of students' chests in detecting tuberculosis over the method of physical examination alone used in the decade previous to the present study.

Myers and Wulff<sup>22</sup> give their observations on tuberculosis in students at the University of Minnesota for the last eleven years. Since 1928 tuberculin testing has been routine on all entering classes. About one third of the students react positively. The cost has prohibited x raying all the positive reactors but many have been done at the students' expense. Since 1929, routine x raying of the entering classes to the School of Nursing and School of Medicine has been practiced Lach year a new film has been made so that senior students will have been x rayed at least four times. It is hoped to extend this service to

all classes in the near future By this method it has been possible to determine almost exactly when intection has occurred in these two precarious professions, and to trace the source of infection with considerably less difficulty

Prior to 1928, the method of finding cases of tuberculosis among the students was to wait for them to present themselves for examination because of illness. Several cases are cited to show the faults of this latter plan. Frequently the disease had progressed to such a far advanced stage when the diagnosis had been made on physical signs and symptoms that death or very serious illness was the inevitable result Furthermore, such individuals were frequently spreaders of tubercle bacilli among their fellow students on the campus. In the future, it is the plan at the University of Minnesota to test all entering students with tuberculin, x-ray the positive reactors, and repeat the testing on all negative reactors at intervals throughout the university course.

Other surveys have been reported, particularly among the Indians in the Midwest and Northwest, and among the Orientals, but perhaps the above citations are sufficient to show that a real beginning has been made with modern weapons in a direct attack upon the strongholds of tuberculous disease. It is certainly to be hoped that other states will realize the value of this splendid work, and embark upon programs that have as a goal the eradication of tuberculosis within their borders.

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"16 EQUITABLE BLDG

### American Academy of Pediatrics

### Proceedings

# THIRD ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

Monday Afternoon Session June 12, 1933

#### Round Table Conference on Rheumatic Heart Disease in Children

The meeting was called to order at 2 15 PM in the Berwyn Room of the Edge water Beach Hotel by the Chairman, Dr. Hugh McCulloch, St. Louis, Mo.

DR HUGH Mcculloch—This conference on rheumatic heart disease is to follow the one held last year under the direction of Dr Morse. The general subject of rheumatic infection was covered by him and many important questions relating to diseases of the heart were presented. In order to continue the discussion, it has been deemed wise to present four principal articles and to limit discussion to these I have therefore selected four separate articles, each of which is somewhat different and yet all are related.

First A definition of what the rheumatic state or rheumatism means

An antigen (toxin) formed by recurring infection in one or more areas of the body (sore throat, common colds) and operating in an injured host (malnutrition) produces fixed (proliferative) and/or wandering (exudative) tissue response in the various susceptible parts of the body

- a. Tonsillitis/nasopharyngitis (sore throats, colds)
- b Arthritis (joint pains)
- e Carditis-mio, endo, peri (heart disease)
- d Encephalitis (chorea)
- Nephritis
- f Pneumonitis
- g Peritonitis

The second article for discussion would be the factors which influence the manifestation of rheumatic fever and heart disease in children

- 1 Type of response shown by the patient
  - a Sensitized individual (exudative)
  - b Desensitized individual (proliferative, hyperplastic, aplastic)
  - c Nonsensitized individual
- 2 Age when the first attack occurs
  - a Progressive and recessive growth of tissue
- 3 Race.
- 4 Climate
- 5 Social status.

The third article is the cure of children who have rheumatic heart disease

- 1 During the period of active infection.
- a. Evidence active focal infection fever rheumatic nodules
- b Treatment, clean out foci of infection Salleylates rest Congestive failure
- 2. During the period of convalencence
  - a When does it begin. Normal temperature and pulse rate. Good appetite no fatigue
  - b Criteria of satisfactory progress Gain in body weight and height to expected normal. Freedom from infection.
- 3 During the period of quiescence
  - a. Avoid infection by contact.
  - b Daily routine balance of activity and rest.
  - c. School and/or work. Desirable Fitting for life work. Learn limitations.
  - d General health. Food calories, variety vitamins, fluid. Sunlight, fresh air Quiot, sleep
- 4 The time when they become healed, or we think they are cared.
  - a. Prognosis Myocarditis, Endocarditis (nortic and mitral) Pericarditis.
  - b Probable chance of recurrence

The fourth article is the discussion of the relation of rheumatic fever and heart discuss in children to heart discuss in adult life.

- Healed juvenile types in adult life nortic and mitral chronic cardine valvular disease.
- 2 Subscute bacterial (streptococcus) endocarditis in old congenital or acquired heart disease
- 3 Myocardial failure after an old myocardial injury from rheumatic fever acarlet fever proumonia influenza, diphtheria syphilis
- 4 Coronary heart disease.

The presentation of the first two subjects will be taken up followed by a discussion before proceeding with Articles 3 and 4

Definition of Rheumatic Infections -It is very apparent that 'rheumatic in fections is an inclusive term used to cover many manifestations of the rheumatic state in different individuals. For many years the term ' rheumatism ' was used to define those conditions associated with painful swelling and structural changes in joints, as well as certain other symptoms and signs more or less related to the joints. Following this early use there occurred a period when an attempt was made to differentiate more clearly the various lesions occurring in rheumatism and there has been a tendency to differentiate these diseases too sharply and to do away with the older term. Since rheumatic infection in children is a process involving many parts of the body in different ways and at the same or at different times it may be advisable to again use a single term rheumatism' or fection ' or the ' rhoumatic state to include these various protean manifestations Since heart disease is such a constant and important manifestation of rheumatism in children it may be advisable also to include "rheumatic heart disease ' as a general term of the same nort as the others. The decision as to which term is best will probably rest with common usage and not come about by any special edict or order

The following definition of the rheumatic state is now proposed for discussion. An antigen (toxin) formed by recurring infection in one or more areas of the body (sore throat and common colds) and operating in an injured host (malnutri tion) produces fixed (proliferative) and/or wandering (exudative) tissue response in various susceptible parts of the body "

The nature of the antigen producing the changes in the body is not vet certain Investigative work done so far indicates that this substance is not of the nature of a filtrable virus, though this possibility cannot be finally dismissed. Recent studies on the virus of the "common cold" reported by Dochez may have some bearing on a virus of a similar sort being the antigen of rheumatic fever. The experimental evidence suggests that it is a bacterial product of the general order of toxins formed by streptococci growing in some focus, usually in the nose and throat area. Specificity for either the toxin itself formed by the organisms or for the organisms themselves has not been proved. Indeed, the more recent bacteriologic studies of Swift and others seem to indicate that many organisms may be responsible at times, or that one organism may liberate different toxins at times.

The nature of the infection which liberates the antigen varies a great deal, it may be a single infection in the tonsils or recurring infections of varying severity in the nose and throat area, or it may be located in other parts of the body. The tonsils, the nasopharangeal mucous membrane and the sinuses, however, seem to be the usual areas involved. This infection may manifest itself in different ways, either as sore throats, common colds, corygas and tonsilitis.

Malnutration must play an important part in determining the incidence of rheumatic infections as well as their manifestations in a given child manifests itself in children in many ways, all of which are more or less familiar to us and need not be discussed fully at the present time. It has been our observa tion in a large group of cardiac children that most of them give a history during infancy and childhood of improper feeding, housing, general care, and of recurring infections of the type usually considered to be associated with a low body resistance and malnutration How important this association may be is difficult to prove Its high incidence, however, suggests a probable close relationship. The usual con ception of malnutrition in children is that of underweight and undernutrition with a low body resistance to infection. It should be pointed out, however, that quite frequently children may be obese and suffer equally from malnutration and low We have observed this type of malnutrition very body resistance to infection frequently in children with chores

The nature of the manifestations of the rheumatic state in children varies, and may be of two general types. First, a response on the part of the fixed tissue elements of the body, producing structural changes in the various parts of the body, particularly the heart. These have been classified by Swift as proliferative changes. The essential process is the formation of rheumatic nodules (Aschoff bodies), together with changes in the heart muscle, in the valves and the pericardium. These lesions occur also in other parts of the body, particularly in the brain and lungs. The second type of response is due to changes in the wandering tissue clements of the body, characterized principally by acute transient exaditive processes such as leucocytosis, fever, edema, etc., in joints, heart structure, brain or skin. While these two types can be well defined and frequently children may be seen who belong entirely to one or the other type, there may be children who show signs belonging to both types who, therefore, are mixed. The exact chinical differentiation at times, therefore, may be difficult

While manifestations of the rheumatic state occur in many parts of the body, there are certain principal locations where it is usual to find either or both, proliferative and exudative changes

n. The tonsillitis and/or nasopharyngitis is regarded as the initiating cause of an attack of rheumatic fever and serves as the focus of infection from which the antigen is liberated. It also seems probable that the inflammatory changes in the tonsils and/or nasopharyny may be a manifestation of the rheumatism itself. Full

discussion and investigation is very much in order on this point. It may be pointed out that a child who suffers from rhoumatism should be seen by the attending physician during the time when the soute process in the nose and throat area is going on in order to determine the appearance of the lesion then has well as in the interim between attacks. It is only in this way that a proper classification of this process can be made.

- b Painful joints are a common manifestation of rheumatism from which the condition derives its important terminology. When true joint pains occur in children they are usually due to rheumatism and except for the occasional small child who has a "septic arthritis rheumatism should be suspected in all who complain of joint pains. Opinion today definitely excludes growing pains as a manifestation of rheumatism indeed, there should be serious question as to whether pain can result from growth in any way. Its further use should be discouraged. The most important pain in the extremitics occurring in children not due to rheumatism is that which results from fatigue. In our opinion, this type of pain is very common and simulates closely that of rheumatism. It usually occurs at night after going to bed, is usually in the lower extremities and is not associated with other signs of rheumatism. It is described by the child as a norceas in the legs and does not occur in the region of the joints. In such children flat feet must be considered also
- c The manifestations of rhemantism in the heart are so well known that they need not be discussed here. Suffice it to say the three important regions of the heart are usually involved and in a child who has repeated attacks of rhemantic fever one may safely assume that the endocardium and the myocardium are always involved, and that sooner or later the perleardium will show changes. The term earditis is used frequently by pediatricians to indicate the widespread changes or curring in the hearts of these children. Endocarditis should mean rhemantic heart disease with endocarditis.
- d. Chorea is frequently found in connection with rheumatic manifestations and more and more is boung looked on as a specific type of encephalitis due to the action of the texin in the brain, particularly in the lower basal nuclei. These changes in the brain usually are of the exudative type though occasionally rheumatic nodules and proliferative changes may be found.
- e The relationship between inflammatory changes in the kidney due to infection and rheumatism is not so clear. It has been our observation that children with rheumatic heart disease show some form of nephritis more frequently than a normal group and it also as well known that children with nephritis resulting from infection in the nose and throat frequently may have important structural changes in the heart. When these changes occur they are of the type usually found in acute rhoumatic fever. The relationship may not be close but there are certainly many similar points. Children with nephritis do not show rhoumatic nodules in the kidney tissue though the crescent changes in the glomeruli may at times simulate this same process.
- f In the last ten years pathologists have pointed out lesions in the lungs and plears which probably are of a rheumatic nature. Structures resembling Aschoff bodies have been found and the interstitud change in the lungs and plears bears many resemblances to the lesions in the heart muscle and endocardium. Von Glahn and Pappenheimer have pointed out the probability that pneumonitis and plearities of this type may be a manifestation of rheumatic fever.
- g Certain cases of paritonitis have been reported in which it seems probable that the lesion was due to rheunatism. These case reports so far have not been frequent though it is quite possible that many of them have either been overlooked or have not been investigated with the idea of a possible relation to rheumatic in fection. This point can be carefully investigated when suspicious cases occur

Factors Influencing the Incidence and Manifestation of Rheumatic Fever and Heart Disease in Children

- 1 It has been pointed out by Swift that the nature of the rheumatic infection varies with the type of response shown by the patient to the infection. In individuals who have been sensitized previously to streptococcic infection, particularly adults, in attack of rheumatic fever manifests itself principally by exudative signs, especially painful joints, with redness and swelling, fever, leucocytosis, prostration, and by acute myocarditis, endocarditis and pericarditis. It is also known that such an individual tends to show well defined attacks of rheumatic fever with a period rela tively free from activity in between These cyclic attacks are not seen commonly in children. It also has been shown that individuals who have been sensitized to streptococcic infection, probably will show proliferative changes of a hyperplastic type, especially rheumatic nodules. Aschoff bodies, chronic or subacute myocardial, pericardial and endocardial changes and pneumonitis. This type of response can be reproduced satisfactorily in laboratory animals. In the non sensitized individual, the proliferative response is usually aplastic in nature and not associated with the formation of rheumatic nodules and Aschoff bodies, but with a progressive injury described by Swift as a "cachectic" or "anergic" type. It is this type which we have seen frequently in very young children during the first attack of rheumatic fever, and with a fatal termination
- 2 The age of the patient when the first attack of rheumatism occurs apparently determines to a considerable extent the manifestations of rheumatic fever. During childhood the process is apt to be widespread throughout the body as well as in volving all parts of the heart. It also is during this period that the joint pains are less severe and less constant and in early childhood, particularly under the age of two, joint pains rarely occur. During adult life the joint pains occupy a much more prominent part of the picture of rheumatism and the disease is more localized in any tissue. It is also well known that the chance for the heart to be involved during adult life is much less than during childhood. It is interesting to note that certain adults may show the same form of rheumatism seen during childhood. It is probable that these individuals have never had an attack of rheumatic fever or an infection of this type previous to the onset of the disease. We have had oppor tunity to observe on several occasions, children who have shown attacks of rheumatic fever similar to that seen more frequently during adult life. These children in each instance have shown other signs of biological maturity and growth, so as to make it seem probable that the nature of their rheumatic attack was determined by an early maturity This difference in age periods needs further study and clarification It is suggested that the important subject of the nature of growth may determine itself the type of response shown by the patient. It is quite possible that during the period when progressive growth is taking place, i.e., an increase in number, size and function of cells, the manifestations of the disease will be influenced to a con siderable extent by this factor Likewise, during the period of life when recessive growth is occurring, i.e., decrease in size, number and function of body cells, other manifestations may present themselves because of the different type of growth It must be pointed out in this connection that the human body shows both types of growth at any given period of life, that while progressive growth predominates during childhood, there are certain recessive changes taking place also and likewise during adult life after maturity, recessive growth predominates, there may be certain progressive changes occurring simultaneously. This important sub ject needs investigation in the light of more recent studies on the nature of growth
- 3 The influence of race on the manifestation of rheumatic fever has been con sidered for many years, and recently important information has been developed on this point. While certain races seem to show a lower incidence of the disease,

it seems more probable that this is due to a difference in location rather than a difference in race. Roccatiy Porto Ricaus living in New York City have been found to show a high incidence of rheumatic fever, whereas when living in their native state the disease tends to be rare. A group of New York children with rheumatic heart disease, including several Porto Ricans were transplanted to Porto Rico for a year and during this period the signs of rheumatism disappeared. When these individuals returned to New York City the disease reappeared. Such studies tend to show that race is less of a factor than location.

- 4 The question of climate as a factor in the incidence of the disease has also been considered for a long time and at present is not solved. Rhumatic fover with heart disease is found more frequently in the north temperate zone throughout all parts of the world than in any other location. There is also an opinion that the disease is found infrequently in the southern parts of the United States, in the troples and in similar climatic zones in the southern hemisphere. The disease is not frequent among the Chinese living in the north temperate zone nor is it frequent in South America and Africa. The few observations made in these remote parts of the world however do not entirely settle this important question and further study is needed.
- "The social status of patients with rheumatic fever is generally low and in a recent report from Dr Paul from New Haven it was shown that the disease oc curred more frequently among Yale University students who had come from a lower social status. A definite opinion on this general subject, however is not available and certainly it warrants further study. It is probable that important secondary factors enter largely into the high incidence of the disease in the lower social strate for example bad housing, frequent infectious close contact with bacterial carriers and improper care during minor illnesses, particularly ordinary colds. The importance of these secondary factors in the higher incidence of tuberculosis is well recognized and they probably play an equally important part in the higher incidence of thematic heart disease.

This covers the first two articles of the outline and Dr Bachmann will introduce the discussion.

DR HARROLD A. BACHMANN (CHICAGO) —I have not attempted to agree or to disagree with the things Dr McCulloch has said in his paper but as I read it over I felt there were certain clinical factors which it might be well to review

Dr McCulloch s paper is so clearly conceived and so thoroughly logical that it is difficult to know where to begin this discussion. Of one thing I am sure that in the main most of us agree with the statements he has made and few will take serious issue with the conclusions he has drawn. In regard to the usage of rheumatism in our terminology I feel strongly that it should be retained. If nothing more it conveys to the laymen a striking symptom which should be urgently impressed upon them at all times. Our success in this field of cardiac disease in children still lies in its prevention, and without descriptive terminology we cannot attempt to accomplish our purposs.

It would seem to me, in spite of the completeness of Dr McCulloch's definition of the rhounatic state, that there should be added some statement to the effect that the culmination of the entire rheumatic picture is definitely associated with environmental, chinatic and hereditary factors. Without these, the rheumatic state, one might say, could not and does not exist.

I feel that one point further should be made regarding the rheumatic infection—once it has been inflicted upon a child we should never consider it as cured, but rather as in tuberculosis, consider it quiescent, or as an arrest of the process."

The broader view regarding the etiologic factors, as expressed by Swift, is highly commendable. It logically explains the bacterial differences of the past, and presents a working basis with which to start

I am fully in accord with the opinion that malnutration is an important contributing factor in the production of rhoundid infections. The question that comes to mind, however, is, should we stop here? I am convinced that there are contingent factors of environment which are equally important. Many of these have been strongly emphasized in the current literature. The contagious factor, and the indulgent care of the parents to minor infections should receive additional consideration and discussion.

In regard to the manifestations of the rheumatic state I feel that tonsillitis should be further qualified. Among ourselves and certain economic groups, it may be well to emphasize tonsillitis in relation to rheumatic heart disease. With the average private practice group this emphasis should be guarded. People are so health conscious these days that it behooves us to be careful not to add another worry to the now anxious pseudoscientific mother.

In considering joint and muscle pains 1 am sure we are all convinced of the importance of any arthritis symptoms in childhood. I do feel that every joint pain should be considered rheumatic unless otherwise proved. I wonder, however, whether one should assume a totally benign attitude toward growing pains. Fatigue, as stated, is a rational explanation for some, likewise is the disproportionate growth during adolescence. But eliminating both of these, can we entirely ignore the his tories so frequently obtained?

In this connection, I am going to read the abstract of the paper which Levine of Boston is giving at the American Heart Association Meeting "Recent years have seen concentrated interest in the streptococci as a possible cause of rheumatism Recognizing the importance of this work, clinical experiences indicate that changes in the internal environment of the host must play a very significant role, and this aspect of the problem has received little attention The strong familial factor which cannot entirely be explained on the basis of contagion and external environ ment suggests an inherent vulnerability. There is much we observe that points to changes in the endocrine balance as a factor in deciding whether an individual is The term 'growing pains' has more than colloquial vulnerable to this disease meaning when the problem is viewed in this light, for thus it may be related to the endocrine system. It is also curious that choren practically never returns after the age of twenty except under one circumstance, pregnancy Here again the endocrine Furthermore, there are frequent instances in which recurrent rheumatism appears in the same individual the same month of the year, particularly February We now know that the weight of the endocrine glands alters during dif ferent months, and in February some of them are at a particularly low ebb may be a fruitful field for investigation "

Back in 1909, Sir Norman Moore said "It would be very much more accurate to regard the carditis as the center of the infection and polyarthritis and choren as complications. The joint lesions attract immediate attention by the pain they cause, the movements of choren are not likely to escape notice, but it is the carditic lesion which shortens life" All of us, I am sure, have had thus dictum exemplified in practice, and further discussion of this phase would seem justified

The mention of pneumonitis in association with rheumatic heart disease should stimulate an expression of opinion regarding the posterior lung findings in perientalis. Certainly these findings cannot be entirely explained on the basis of effusion or compression. The clinical course prompts me to conclude that we are dealing here with a pneumonic process due to adjacent pathology.

Dr McCulloch makes the statement that during adult life the joint pains oc cupy a much more prominent part'—and further—'It is also well known that the chance for the heart to become involved during adult life is much less than during childhood' I have frequently been impressed with the same fact in children. In other words when the arthritis symptoms were most prominent and fulminating the milder was the resulting carditis. Is it that the infection spends itself here and thus lacks the potney to invade other susceptible structures?

The influence of race on the manifestation of rhomatic fever is sufficiently covered by Dr McCulloch a concluding statement in that studies tend to show that "trace is less of a factor than location." I would, however, raise the point that in my experience the Italian child with heart disease shows the most remarkable come back of any race I encounter Lakewise that the Negro race, even in the North, seems less vulnerable to the rhomatic infection.

Much has been said regarding specific phases pertaining to the rheumatic state in childhood but the most important point to me is the social status of the patient. Were it and its contingent factors explained, I am sure we could forge ahead with one of the most striking examples of preventive medicine known in history. Our success must lie in the prevention of heart disease among children, not its cure. If we could once analyze and explain these environmental factors we would begin to accomplish results. Why is there such a dearth of rheumatic heart disease in private practice and why such an abundance in our dispensary groups? Does sensitivity allergy and heredity explain all? Certainly no field of investigation could be more fruitful and helpful than further study of the environmental factors per taking to the rheumatic state and rheumatic heart disease in children.

DR McCULLOCH —One of the main ideas in these conferences is for each of us to express his own experience and the opinion formed as a result of that experience. By this all of us learn what others are doing. We would like to hear from as many as eare to discuss any particular phase of the presentation thus far

DR. T. D. GORDON (GRAND RAPES, MICH.) —Besides the ordinary chorea are there any other brain conditions which are considered as being rheumatic—meningitis for instance?

DR. ROBERT A BLACK (CHICAGO) —I feel that a great many headaches in children might be looked upon as rhoumatic in character. I personally have never seen meningitis that I would say was rhounate. We all see many cases of chorea which resemble a mild encephalitis. In fact, I think it is hard to differentiate a severe type of chorea from encephalitis.

DR. BACHMANN -What prompted your question?

DR. GORDON—A case I recently saw—a child who had rheumatism, and who in my absence from the city was taken to the hospital with meningitis—2,000 cells mostly polymorphonuclears but no organisms were found on six lumbar punctures. This boy made a complete recovery without other treatment than salleviates.

QUESTION -Did you make cultures of the spinal fluid?

DR. GORDON —les and no organisms were obtained. I returned to the city after four or five days, and knowing the history of the case suggested the treatment and the boy made a rapid recovery without any residual signs from the meningitis.

DR. PHILIP ROSENBLUM (CHICAGO) —One should be very careful in interpreting a 2000 cell count. The patient may have had an epidemic meningitis, that alone does not speak for rheumatic involvement of the brain. One might have rheumatism and also have a meningitis of other origin.

The broader view regarding the etiologic factors, as expressed by Swift, is highly commendable. It logically explains the bacterial differences of the past, and presents a working basis with which to start

I am fully in accord with the opinion that malnutrition is in important contributing factor in the production of rheumatic infections. The question that comes to mind, however, is, should we stop here? I am convinced that there are contingent factors of environment which are equally important. Many of these have been strongly emphasized in the current literature. The contagious factor, and the indulgent care of the parents to minor infections should receive additional consideration and discussion.

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Body weight alone does not constitute a good criterion of malnutrition even when considered in relation to lody height. The obear child is frequently as much unalnourished as one who is underweight. We have seen many children with choren who are fat but on close examination it is easy to recognize that they are mal nourmhed just as much a those who are underreight. Our impression is that chorea occurs in the obese twic of older child more than in any other constant type. I seriously question whether rheumatic fever and especially the heart disease that goes with it will occur in a child who is in good nutrition. I do not mean that all children who are malnourshed have or may have heart disease. It has been observed also that many tuberculous children are normal in weight and that the incidence of underweight among tuberculous children is very low but again in these studies, the sole criterion of malnutrition was underweight without regard to other manifestations of malautrition. I think a full clear definition of nutrition would possibly help us a great deal in interpreting what constitutes malnutrition are certain other diseases like rickets in which the children are not always under weight but should be considered as malnonrished.

DR W 4 GIBSON CHICAGO-What are the enteria for the determination of mainstrition in children?

DR McCULLOCII -That is a rather difficult question to discuss at this symposium and in se short a time. Nutrition is the state in which living matter exists at any given time resulting from the various processes of metabolism. As well as one can define this sta e in living children under ordinary conditions, the criteria are (1) an estimation of hody weight with some other mass measurement in rela tion to body length or some other linear measurement using the many and varied tables that have been described for the establishment. I normal or average ratios making allowances for those influences which deflect the individual from the normal or average (2) an examination of those parts of the body which are susceptible to nutritional changes and which are evident on ordinary physical examination the various qualities of the akin the amount obsistency and distribution of subcutaneous body weight and the size tone and coordination of skeletal muscles (3) by some knowledge of the child a history in regard to environment type of feeding intake of necessory food elements reaction to infection and other general habits of play rest school etc. Further than this the question becomes very complex and involves the determination of many points in metal olic and chemical Inhoratories

DR. ALBERT D KAISER (ROCHESTER N. 1)—I want to say something about growing pains in contrast to fatigue pains. I have I cen interested in growing pains as to whether they are supploms of chemantic disease or whether they are all fatigue pains. I followed a number of children over a period of years with a history of growing pains and no other rheumatic symptoms. In this large group of children if found that 10 per cent of the children who had growing pains appeared later with some involvement of the heart in most instances not sever. They had a mild earline involvement vet severe enough to be classed in the group of children having rheumatic carditis. It is of course not certain that the growing pains were responsible for the cardine involvement but it is suggestive that persistent growing pains are the result of an infection. I found that 8 per cent of the children examined in Rochester gave a history of growing pains. A higher in idence of growing pains has been reported from other cities.

I am not in absolute accord with the statement that rheumatism is influenced chiefly by the social environment. It plays an important part but another significant factor seems to be necessary and that is the element of infection. Those who have followed Coburns' work in New York have been impressed with his studies on

nurses, training in the Presbyterian Hospital. Before completing their course 30 per cent had developed some form of rheumatic manifestation. He concludes that it is not so much the change of environment for they had adequate food and rest, but because they were brought in contact with streptococcic infection which they had previously escaped. The incidence of rheumatic fever has been high in Rochester during the last two years. There has also been a high incidence of scarlet fever It was found that many children who appeared with rheumatism had scarlet fever within the last three years and the cultural studies of the throat flora showed a high incidence of hemolytic streptococci. The evidence at hand seems to suggest that poor social environment plus contact with the streptococcus is a factor in the causa tion of rheumatism.

I believe the improvement noted in children sent to Porto Rico is due to the absence of streptococci in the throat. The streptococcus is probably the exciting cause of the disease but a susceptible host is necessary. The factor involved rendering the host susceptible is not known. It may be some enzyme or internal secretion that fails to function properly.

DR J R GERSTLEY (CHICAGO) —I have always been interested in the subject of growing pains. Every child seems to have them to some extent. When Dr Kaiser reported a history of growing pains in a large percentage of rheumatic children, did he have any controls?

Of course I realize that Dr Kriser's study was not one primarily of growing pains. These were reported as purely incidental findings. However, growing pains are such a common complaint that I believe we should be somewhat critical as to their significance. For instance, if Dr Kaiser reports that 10 per cent of his cases of rheumatic endocarditis gave a history of growing pains, what percentage of a like number of children without rheumatism and endocarditis would give a history of such pains? If a number of much less than 10 per cent would be found, I grant the evidence would be in favor of a rheumatic significance to these pains. But I do believe there should be a control series

DR McCULLOCH—In reply to Dr Gerstley's question, we have seen children in the clinic with rheumatic heart disease, oftentimes in an advanced stage with no history of pain in the joints, growing pains or any other kind of pain. The difficulty we have had is to know how to classify in an intelligent way the various pains these children may have. It is well known that they vary a great deal in degree, location and in many other characteristics. The well defined inflamed joint seen so commonly in adult life with the usual objective signs is relatively infrequent in younger children. Mention has already been made of the pain in the legs from flat feet and it may be pointed out again, the rather common pain in the legs from fatigue. These pains should not be considered either growing pains or rheumatism. The chief difficulty arises when a child is seen with tonsilluts, with signs of heart disease and with ill defined pains in the extremities. Such pains are probably due to rheumatism and should be so interpreted. I would like to insist again that mere growth should not produce pain in any form.

DR ROSENBLUM—One thing I would like to ask, is about erythema multiforme associated with arthritis, as a rheumatic manifestation. This association is more frequent than we realize

DR McCULLOCH —The list of manifestations of rheumatism as given is, of course, not complete I agree with you that crythema is a fairly common sign.

DR EPSTEIN—Skin lesions are certainly a manifestation of rheumatism. I think you see them in children who have rheumatic nodules if the skin is involved in some form by the rheumatic infection.

I hoped somebody would bring up the question of crythema nodosum.

DR G R WEINFELD (CHICAGO)—In reply to Dr Rosenblum's question, Swift pointed out that this was also a manifestation of very serious cardine involvement I have had about six cases under observation for about four years who have had erythema annulare One boy has had it for about six years. He has no serious cardiac complications. At one time it appears as a coincident manifestation, its intensity depending upon the intensity of the infection. Then for a time the dermatitis disappears and again he will have the dermatitis without anything clae. In one child with a severe heart lesion an erythema marginatum has been present for a long time. The other day I saw another child who had an erythema marginatum but I had not noticed it until I saw him in a strong light. I doubt very much whether it is a proliferative lesion. It has more the carmarks of an allergic manifestation. I think it is important that we all understand what we mean by this lesion.

DR ROSENBLUM—Rheumatic peritonitis may occur but surely not very offer. The majority if not all of the cases were associated with periterridita. We know one of the first symptoms of periearditis is often pain in the abdomen, and not infrequently they get to the surgeon first who operates only to find a pericarditis later. We know these cases do not need operation. Surgeons usually justify their operation by stating there was a peritonitis. They never obtain positive cultures and all the cases heal without drainage.

I feel the majority of these so-called operated rheumatic peritoritis patients are just a mistaken diagnosis for beginning pericarditis. I question, too the occurrence of real rheumatic pneumonia. I feel much as does Dr B. Gibson about the etiology of rheumatism. There is probably a specific organism as in tuberculosis with environment diet vitamins, climate etc. only secondary factors.

DR. BACHMANN —I think Dr Kaiser mentioned a very important point 'exposure to germs. We see this frequently in the form of epidemies. I think there must be something else associated that is, the lack of proper attention to minor infections. The children we encounter in private practice receive attention for minor aliments and thus evade serious trouble. In the dispensary group these are ignored. I have felt that the indulgent care toward these minor infections, especially exposure to streptococcus, plays quite an important part.

DR J H WALLACE (OAR PARK)—All this confusion about some of these things prompts me to challenge Dr Bachmann's optimism about prevention. There is a good deal of conflict of opinion about race and hereditary and churate. In discussing malnutrition Dr McCulloch thought the definition should be emphasized. I feel the same way about prevention. The preventive phase of the problem as I see it is the following through in the prevention of the second attack or prevention of complications in the heart. If by prevention of rheumatism one means prevention of the first attack I cannot feel the optimism of Dr Bachmann since we are not agreed as to the exciting cause. It would seem that prevention strictly speaking would entail eliminating the predisposing factors—a rather gigantic task if it means changing racial and hereditary characteristics and bringing up the housing situation and hygiene of the lower social strata. One thing I might mention with regard to race and color is that it is very difficult to infect an African Negro with scarlet ferer and the Chinese are only slightly susceptible. This might have something to

do with the fact that they are less susceptible to heart disease, since immunity to one streptococcal infection seems to involve immunity to other strains of streptococci.

DR BACHMANN—My optimism is simply the desire to educate the laymin with the ficts about rheumatism. The average parent who comes to us today with a child with heart complications has no idea as to what that might have come from

DR WALLACE—That is probably correct. We cannot prevent rheumatism, however, until we know more about it. We can prevent the second attack. Strictly speaking, so far as the prevention of rheumatism is concerned, I wonder if we know enough about it

DR BACHMANN -I feel that prevention will come before the cure, however

DR GIBSON—Dr McCulloch has had control over his patients for a long time and I wonder if, after a number of years, these children have had definitely fewer recurrences than other children not so well cared for

DR McCULLOCH -That is a hard question to answer About five years ago, we reported the results of a study of a group of cardine children who had been patients in our convalescent home. Much to our surprise, we found that the number of attacks of rheumatic fever in the children who had received such care tended to be rather high after discharge to their homes, in comparison with a similar group who had not been admitted to the convalescent home. We felt, however, that the child's general condition had been greatly improved and that when the subsequent attacks occurred, they were of shorter duration and there was less involvement of the heart. Our only explanation of this observation was that when the child returned to his previous environment, particularly if the environment had not been improved, exposure to further infection resulted in attacks of rheumatism because his susceptibility had not been altered. The study led us to believe that convoles cent care was of value chiefly during the time the child needed to be in a more favorable environment and also in rendering him more able to withstand subsequent infections It still seems to us that the prevention of rheumatism lies first, in creating healthy children through the application of the broad principles of pediatric care, second, in taking care of children properly when they have an acute illness and, third, to be sure they are well of any infection before they return to school. I think these things he distinctly within the field of pediatric care and have no more relation to cardiac problems than they do to other forms of disease. In this way, we will be able to prevent a lot of rheumatism

DR J C McKITTERICK (BUILINGTON, IOWA)—I am inclined to agree with Dr Wallace as to the importance of prevention. When a patient comes to me with swollen joints I know he has rheumatism. He complains of stiff legs in the morning, has low fever, and fatigue, this leads me to believe that the child may have rheumatic heart disease. But what will prevent it? Until more work is done in the prerheumatic stage I think we cannot get very far

DR KAISER—Might I state our own experience. We had the same feeling that individuals with rheumatic disease had low calcium and cholesterol values. We studied the blood lipids in 75 rheumatic cases, and found normal calcium values and the cholesterol was well within normal limits. They were low in the acute cases but they were also low in pneumonia and scarlet fever, but with recovery they returned to normal. Dr Clausen studied the vitamin A content and the carotene in the same group but found no striking relationship between the rheumatic state and a deficiency of this vitamin and provitamin

DR. McCULLOCH —Balanced feeding and proper dietary intake are of course important. A survey of the duct of many of these children shows a history of a predominating brend and butter diet with relatively little milk meat eggs and vegetables. The mother often explains that the child eats enough but runs it off, ' which is, of course not true. Unfortunately this same explanation is offered many times by physicians for the malnutrition underweight and fatigue which may be present. Activity should not produce mainutrition and it is probable that with satisfactory food and regulation of activity the child would not become thin. The improvement following administration of foods containing abundant calcium saits and cod liver oil often demonstrates that the diet was defective

We now come to the third part of our presentation—The Care of Children II the Rhemiatic Feter and Heart Disease. It should be clear to everyone that the care of such children depends on the period in the course of the disease in which the patient finds himself. It is probable that a lack of consideration of this important subject accounts for the widespread divergence of opinion which exists in the minds of most of us and for the unsatisfactors directions for care that most patients receive Measures which are applicable at one time would be inappropriate at others. It is suggested that four important periods in the course of the disease should be en sidered (1) The period of active infection (2) convalencence (3) quiescence (4) when the process is healed or when it has disappeared and the patient is cured

- 1. During the period of active infection evidence of activity must be sought and recognized. The three important points of evidence would be active focal infection in tonsils, sinuses or in any location, fever and rheumatic nodules long as cervical glands remain enlarged the tonsils show evidence of redness edema, thickening and pus or so long as the mucous membrano of the nasopharyax shows hyperplasia, redness, edema etc. the patient must be considered to be in the period of active rheumatic infection. Also so long as the body temperature remains above normal or shows extreme daily variations the patient should be considered in the period of active infection. Lencocytosis and joint pains are of value when they are present to a marked degree but in the usual child their absence or presence is not of great assistance in determining the period of infection. Rheumatic nodules, however are definite evidence of an active infection and so long as they remain it must be assumed that an active process is going on in the heart. During the period of active infection treatment should be directed toward the control of those manifestations present. It is important during this period to clean out foci of in fection as soon as it is determined that the patient can stand the necessary procedures. The use of salierlates and other drugs relieves fever joint pains, and many other toxic manifestations. It is also important during this period to provide rest for the body and heart as much as possible. This important measure enunot be exercipleasized even though it is briefly stated here. If congestive failure of the heart occurs during this period it is of grave prognostic significance and should be a matter of first consideration. So long as the heart muscle is unable to do its work, it is futile to undertake other remedial measures
- 2. It has always been difficult to decide accurately when patients are getting well and are convoluenced. In a discuss like rhounatism where the symptoms and sigms are so varied and irregular it is very much more difficult than usual. Some of the difficulty arises from the fact that few criteria are available to determine accurately the absence of infection. It has been suggested that a normal temperature and heart rate together with a good appetite should indicate recovery from any infection. These statements should hold true for children with rhounatic heart disease. In addition children should show no sigms of fatigue should be gaining in body weight and height and should be free of active infection in tonsils and

elsewhere Other criteria such as the absence of leucocytosis, changes in the heart signs, etc, are also easily applied to the individual child during the period of convalescence Griduated return to normal activity and function should be undertaken. Whether or not this period is short or long will be determined by the degree of injury occurring in the heart and body during the attack. It must be pointed out that there is a tendency to err on the side of a convalescence too short rather than too long, and in case of doubt it is safe to delay the convalescence

3 By far the largest number of children with rheumatic heart disease are found in a period of quiescence. While those under the care of a physician are generally in the period of active infection or are convalencent, surveys show that a very much larger number may be found in school and not under the care of physicians. This very important group needs careful study and control. These children will be found on periodic health examinations, at school, and when under the care of physicians for some intercurrent condition. It is an important group to recognize, since remedial measures will yield larger returns than in almost any other group under consideration. These children are not ill, but their health is impaired, the chances for a return of the rheumatic fever are good, and the ultimate prognosis for their reaching healthy adult life is poor. Educational measures by individuals, organizations and institutions vill uncover a large number of these children.

Their care consists of a regulation of their daily routine so as to provide a proper balance of activity and rest. When possible they should be allowed to attend school or be at work, and to undertake jobs which are within the limit of their performance Since most of these children are in Class I, they probably need more of an adjustment of their physical activity than a restriction of such activity Such a program seems desirable, because it allows the child to live more nearly normal than when restricted in any fashion, and probably is of greatest value because such children must be fitted for their life work. Unless they can learn their limitations they probably become maladjusted both mentally and physically and acquire an unusual outlook on life as well as their inability to support them selves It also is important during the long period when such children remain quiescent to provide proper measures for good general health By this is meant proper food, proper amount of sunlight and fresh air for play and rest, and enough sleep, and the importance of a quiet environment must be emphasized factor is of some importance is borne out by the high incidence of choren in children living in congested, noisy sections of the city

4 Evidence is available that children with rheumatic fever and heart disease may recover entirely, so that at subsequent periods no evidence of disease can be made out. A larger group definitely are known to live for long periods without recurrence of their rheumatic fever or heart disease. Many of these have been known to be throughout the remainder of a normal span of life, with full physical activity and earning power, with no further heart disease. While this number is relatively small in comparison with the total number of children with heart disease who die early, it is sufficiently great to warrant special consideration portunity rarely comes to the pediatrician because the problems involved are a part of adult life The part for the pediatrician to know, however, is that there is some reward to offer the cardiac child for carrying out the directions Unless this reward can be pointed out, the child may have very little to look forward to and no in centive to carry out instructions. The probable chance of recurrence of a myocardial, endocardial or pericardial lesion is always great Such children must be treated more carefully when infections occur than individuals who have not previously had They must be told they will always re attacks of rheumatic heart disease quire special protection. Children suffering from mitral valvulitis particularly when stenosis has occurred, have a bad prognosis, and Cotton has shown that 90 per cent

of such children are dead after a period of ten years from the onset of their discase Contrary to the usual prognosis of patients with syphilitic acrititis and nortic insufficiency when the prognosis of life is not greater than three to five years, children with rheumatic acrititis and nortic insufficiency uncomplicated by mitral stenosis seem to live and do well, provided the active infection disappears. It has been pointed out by Dr Conner that such individuals may live several score years without explice distress.

DR. BACHMANN—On the care of children with rheumatic fever and heart discase I am sure we are all agreed. Agreed at least so far as fundamental principles are concerned though we may disagree on dotails. However, until facilities are generally available where patients with the varying degrees of rheumatic infection can be cared for complete success cannot be obtained. My feeling is that the chronic cardiac cripple receives too much attention while the milder types and those still considered potential receive too little. The only solution to this question rests in the establishment of more homes or sanitariums for the chronic or perpetual rheumatic thus making available for the others more beds and more extended care. I find myself frequently discharging patients with a promising future and retaining those with none—only because the word is crowded and something must be done about it.

In ascertaining when the acute stage of rheumatism has subsided, I feel that no greater display of the art of medicine exists. We sill have clinical criteria upon which we pin our faith but upon final analysis experience observation and intuition are the factors which guide us most. Among the more recent criteria pronounced as valuable, is that of Bernard Schlesinger in a study of the sleeping pulse rate in rheumatic children. I would like to inquire if any of you have used this method and how reliable it has appeared to be. Personally I attempted it but gave it up before a definite conclusion could be reached. To me the most convincing evidence of heart improvement and integrity whether in the hospital or in the clinic has been weight maintenance and gain. No other functional test in my experience, is more easily obtainable or more reliable.

DR BLACK.—In answer to Dr Bachmann's reference to Dr Schlesinger's observation on the pulse change between the sleeping child and the child awake Dr Schlesinger showed many cases in which his night and day pulse ratio proved the correctness of his statement. At La Rabida Sanitarium we found it to be correct but it was not observed as frequently as Dr Schlesinger seemed to find. We take a midnight pulse in the Sanitarium and find in chorea the reverse is true in chorea a very high day pulse with a low night pulse. The spread of the pulse rate becoming much less as the choree improves

Dr McCulloch does not feel as enthusinstic about the Sanitarium as I do We have had about 1600 cases go through the Sanitarium. We do not have as good a follow up system as Dr McCulloch has

The physicians treating tuberculosis made great advance in arresting the discase when they instituted sanitarium care. At La Rabida Sanitarium we have adopted much the same régime as is followed in a tuberculosis sanitarium. High caloric feeding with much rest and carefully supervised exercise. Until we know more about the etiology and specific treatment of rhounatism I think we would do well to stimulate sanitarium care. You educate the child and the parent as to the true nature of the disease. You are able to detect the slight relapses. Slight upper respiratory infections are often followed in seven to twenty-one days by a recurrence of rheumatism. A rhounatic child who has a slight upper respiratory infection would in my opinion, be much improved if kept in bed until all symptoms disappear which is usually between two and three weeks. Do you not think that by such treatment the later mortality would be much lowered?

DR GERSTLEY—I, too, have been trying the Schlesinger test on cardiac children. Those who are recovering seem to have diminution of the pulse rate at night On the other hand there are a number of fallacies in that test. When you ask the nurse specifically to take the pulse, she is likely to go at it so energetically that she wakes up the child. You must be sure that the child is asleep when the pulse is taken. Whether the interpretation of the drop in the pulse means that the infection is over is another question.

DR BACHMANN—It seemed to me that the count of ten which is supposed to be the difference between the ilert pulse and the sleeping pulse, is too narrow a margin to be reliable.

DR WEINFELD—I wonder whether Dr Kaiser would tell us about his experience at Rochester with tonsils. I would like to ask if there have been any ill effects from the removal of tonsils at the improper time.

DR KAISER—Personally, I am opposed to it, and so it has been done only occasionally. I believe the results are unfavorable. I do not have the data on that.

DR WEINFELD -- When do you feel that tonsils should be removed?

DR KAISER -I have been interested in the relation of tonsils and rheumatism I remember the old textbooks said that the way to prevent rheumatism is to take out the tonsils. When the opportunity came to observe a large number of children that was the first thing I studied, and in my opinion there is no great relationship between tonsils and rheumatism. The important thing in favor of tonsillectomy is that a great number of children are spared throat infections by having an early tonsillectomy Again, statistics are very misleading. We have fried to approach the study from all angles in comparing a large number of children over a long period, those who were and those who were not tonsillectomized. We found 30 per cent less rheumatism in those who had been tonsillectomized-that is, 30 per cent of those children were protected against rheumatism. On the other hand, when we studied the children who had rheumatism, mild or severe, and were tonsillectomized, we could not prove a thing. However, that is my personal experience. I have a letter from Dr Poynton in which he states he could not prove that tonsilications had any bearing on rheumatic attacks, but clinically he saw so much difference that he recommended tonsillectomy I think I feel the same way

DR McCULLOCH—We have been interested in a problem that is related to tonsilication. We have noted occasionally that a child who is either convalescent from or quiescent after an attack of rheumatism, within a week or ten days after operation for the removal of tonsils and adenoids will have an attack of rheumatic fever or chorea. Following the suggestion of Dr. Cameron several vears ago, we instituted the procedure of giving salicylates before operation and continuing them daily for a week or ten days afterward, the idea being that salicylates would probably prevent in some way the rheumatic fever attack following tonsillectoms. It seems to us that the children do not react so much when salicylates are administered in this way.

QUESTION -- How do saliculates act in preventing the attack of rheumatic fever?

DR McCULLOCII—I do not know Nor is it known how they affect any manufestation of rheumatism

DR EPSTEIN—The chairman did not go into detail concerning the manner of administration and the dosage of salicylates. I get satisfactory results by

giving large doscs, 150 grains, per rectum and repeating when necessary. I should like to ask whether this method is preferable to administering smaller doses orally over a longer period of time

DR BLACK.—In cases of active acute rheumatism I give from 40 to 60 grains of sodium sallerlate by rectum for three to five days, then continue with 3 to 10 grains three times a day for six months

- DR A L NEWCOMB (CHICAGO)—1 cannot help but wonder when we talk about prevention of rheumatic fever if treatment and prevention are not much alike. Physicians do not see the children much in rheumatic fever. The parents acall up and directions are given to put them to bed and usually salicylates are given. Sometimes the mother says. I have you every time she has a temperature vet here is a neighbor child who is playing out in the dirt and mud and is never put to bed with a cold. Let it is the neighbor child who develops rheumatic fever. I am usually very careful as to how soon the child is allowed to get up If the parents did not call for medical advice the children would be up and around in a few days. It is hard to separate prevention and care of the rheumatic state.
- DR McCULLOCH —We now come to the fourth article—The Pelationship of Phematic Fever and Meart Disease in Children to Heart Disease in Adult Life This important question has not been solved. Even the usual heart specialist is not familiar with the initial stages of heart disease in children nor does the pediatriclan frequently have an opportunity to observe his patients over long years into adult life. The evidence at hand today is chiefly of the put together variety and is very unsatisfactory. It would be desirable if a large group of physicians, particularly pediatriclans, could observe patients in adult life whom they have studied as children, and in this way learn something of the late effects of heart disease. The following points may be mentioned for discussion
- 1 It would be important to note the number of adults with healed rheumatic heart disease who show recurrences of activity. It was suggested by Dr Morse that chronic cardine valvular disease should not be considered as rheumatic heart disease and that an individual who once had rheumatic heart disease may lose all evidence of rheumatism. However the nature of the heart disease is such that its etiology can usually be recognized no matter at what time of life the patient is seen. It is true that when the active infection in the heart and the rest of the body has disappeared the process in adult life is not similar to that seen in child hood and presents the picture usually described as chronic cardine valvular disease but the origin of the lesion is rheumatic. Proliferative besions of the acric and mitral valves are always important and when destructive changes in the heart muscle have taken place, an injury of a permanent type results. No matter at what period of life the patient may be seen subsequently he will always tend to show characteristic sums and tendencies in the course of the disease.
- 2 Subnette bacterial endocarditis occurs most frequently in roung adults who have either a congenital maiformation of the heart or more frequently an old healed or inactive rheumatic heart disease. Indeed a question has been raised to whether an individual whose heart is normal would ever acquire subneute bacterial endocarditis. There is very little oridence to support such a supposition. Certain investigators believe that the differentiation between subneute bacterial endocarditis and rheumatic heart disease is not great and that they are the same process. The more general opinion, however is that they are distinct processes and the subneute bacterial endocarditis is superimposed on the old healed rheumatic heart disease. The usual organism involved in such an endocarditis is the Streptococcus ciridans though instances of staphylococcus, meningococcus genecoccus and paeumococcus in fections have occurred. It should be pointed out that in voung adults with a

lustory of a rheumatic lesion who have fever and signs of infection, this important form of heart disease should always be considered. It is the usual cause of cardiac death in patients with congenital cardiac malformation, who are free of congestive failure.

- 3 Myocardial failure during adult lite as a result of intercurrent infections or physical strain, particularly during athletic activities, may bear a definite relation ship to an old myocardial injury received from a rheumatic infection or from other similar infections, such as scarlet fever, pneumonia, influenza and possibly from diphtheria. There seems to be little evidence that congenital syphilis affects the licart in such a way as to be responsible for myocardial failure in later life. Or Warthin, however, pointed out that sudden death may occur in adult life as a result of a congenital syphilite infections. This idea has not been borne out by other investigators. The evidence available today suggests that most heart strain occurring in adolescence and early adult life can be traced directly to a history of rheumatism or other similar infection. Investigation of this relationship between the two periods of life should yield important information that would be useful to the pediatrician in directing a child who has had joint pains with or without heart disease.
- 4 Coronary heart disease which includes coronary thrombosis, infarction and occlusion, may occur as a result of circulatory changes in the heart muscle and vessels or as the result of senile changes going on in the body, but it has been suggested that these changes occur more frequently in individuals who give a history either of a high incidence of heart disease in the family or of rheumatic fever or a similar infection during early life. Coronary thrombosis may be a circulatory accident occurring more frequently in obese individuals under great mental and physical strain and hears no relationship to previous heart disease. Since coronary heart disease is an important cause of death, in adult life and particularly among individuals in the higher walks of life, it would seem important to determine the relationship between it and heart disease during childhood. At present this relationship does not seem to be very close

Pediatricians have a large part in the prevention of rheumatic fever, by seeing that children are properly fed and cared for through childhood illnesses, and the mothers become intellectually rich if not financially rich through what we are able to tell them. It is a matter of intellectual status rather than economic status.

DR BACHMANN—I would like to emphasize, in conclusion, one factor regarding the pediatrician, not only in relation to heart disease, but also other chronic ailments of childhood, to say nothing of adolescence. We must extend our range so far as age is concerned. Without this we can never estimate the relation of rheumatic fever and heart disease in children to heart disease in adult life. Neither can we understand the influence an early nephritis has upon the adult. Nor will the adolescent boy or girl receive the intelligent support and guidance so highly necessary at this period. We need adolescent wards, dispensaries and physicians, and it is up to us as pediatricians to demand this extended service and prepare ourselves to handle this now neglected field.

DR McCULLOCH—Doctors particularly interested in rheumatic fever and heart disease who have had the opportunity to follow these rheumatic individuals from childhood into later life are very rare. When the child has been under the care of a general practitioner, he has either overlooked the relation entirely or has failed to recognize the heart lesion. As a rule the information we get from any source is not reliable.

DR BACHMANN -At the present time I am having that opportunity, but I am afraid that I have not been following them long enough to present data of

real value. After the patients leave the Children's Memorial Hospital I have been following them at St. Luke's dispensary to the age of eighteen or nineteen. The one outstanding thing I have noted is that the compensated mitrals and acrites in early childhood seem to have good tolerance and capacity until they get to about sixteen or seventeen and then they suddenly die. That is the only striking thing I have been able to observe up to the present time

DR. EPSTEIN—I have not had this experience. The fact that about the age of twelve, children are transferred from the Pediatric Department to the Cardiac Clinic makes it difficult for the pediatrician to follow cases through adolescence. I think that the only way we pediatricians can determine the subsequent condition of our patients, is by keeping our files and inquiring from time to time as to the general status of their health Recently Dr Morse checked up by this method on one hundred cardiac cases which he had previously examined thirty to thirty five years ago. In some clinics especially in general hospitals which have cardiac departments, I think that it is a mistake to send these patients to the cardiologist. I would rather have the cardiologist come to the pediatric clinic thereby benefiting by his suggestions and at the same time watching the progress of the patient.

DR. McCULLOCH — Dr Luceke I would like to ask you a question. Is heart discuss frequent in Dallast and do you think it occurs among children living in western Texas?

DR P E LUECKE (DALLAS) -I have been practicing there for about ten years and I have seen I think four or five cases of heart disease and to my knowledge no important cases of rheumatic fever at all. I have seen growing pains and occasionally sore joints which probably were due to a mild rheumatism which rapidly cleared up without earding involvement. The cases of cardine involvement I have seen have not been associated with rheumatism, and of the four cases that I recall of cardiac involvement one occurred in a child about sixteen months old who is now eight years old and the murmur is fast disappearing. He had no relapse. The second, in a child two and a half years old, ran a precipitate course and the child died in about four weeks. One other is on the Pacific Coast at this time I any him at about four years, off and on for five years, and he was subchoretehighly nervous with twitchings which were never chorcic the heart was never compensated; the pulse was slow. I do not recall the details of the fourth case We do not see many cardiacs in the hospitals there and do not have the problem of bed space taken up by chronic cardiac cases. I have seen three cases of paroxymnal tachycardia in youngsters, which we thought due to repeated nose and throat infections-had tonsils. After tonsilectomy they gradually improved I have not heard from them for the last two or three years and do not know what de veloped. I do not know whether that had any effect on the rhoumatic infection. The cases of rheumatic fever and heart involvement are comparatively rare.

DR. McCULLOCH -Do you have many children with bad tonsils?

DR LUECKE.-I saw one the week before I came up, but we do not see many

DR. McCULLOCH.—I am always very much interested in hearing someons from regions of the United States like Texas, as to whether these conditions occur in those regions and to what extent

The meeting adjourned at 4 45 PM

and beautiful hall The official dinner of the Congress was held at the Mayfair Hotel, speeches being made by Sir Hilton Young—the Minister of Health—Dr Still, and Sir Thomas Barlow After this function the Government gave a reception at Lancaster House, now the London Museum, which formed the setting for a very beautiful and impressive scene. The guests were received by Sir Hilton Young, on behalf of the Government The Royal College of Physicians had an afternoon reception, the President, Lord Dawson, receiving the guests, and Lord and Lady Howard de Walden kindly entertained members of the Congress at tea in their home, Senford House Sir Gomer Berry and the Board of Management of the Infants' Hospital, Vincent Square, gave a reception in the hospital, and afforded an opportunity of viewing the beautifully arranged new wing just being completed

Dr George F Still is retiring shortly from his hospital engagements, and it has been decided to recognise his retirement in an appropriate fashion. It is proposed that a cot be endowed and named after Dr Still at King's College Hospital, where he has for so many years worked as physician in charge of the Children's Department, Mr Gerald Kelly, an eminent artist, has promised a portrait of Dr Still, provided that a certain specified sum be subscribed for the cot. Dr Still, who was President of the International Pediatric Congress in London this year, is, as is well known, a pioneer of pediatrics in this country, and his retirement from hospital engagements will be deeply regretted by all his colleagues

The British Medical Association held its annual meeting this year in Dublin Dr T Gillman Moorhead, Regius Professor of Medicine at Trinity College, Dublin, being this year's President Dr Eric Pritchard was President of the Children's Section The meeting was a great success, and our Irish colleagues exceeded even their usual great hospitality

KENNETH TALLERMAN, London September 11, 1933

### Comments

THE relationship between pediutries and the 'Child Guidance' clinic and move ment is gradually reaching a sound and satisfactory basis. Viewed from a broad educational standpoint the child guidance movement has been a success, as it has brought needed emphasis upon he importance of the child s behavior and emotional adjustment as well as the physical side of his devolopment.

While the value of the clinic as a propaganda and educational measure can not be questioned, the maintenan c of such an organization as a distinct and separate entity divorced from the established fields of medical activity except in certain specific situations, is neither logical nor sound. The make-up of such an organization composed of a p-diatricelly minded psychiatrist, psychologist, and social workers has proved its value. Such a group attached to a school system for the study and landling of children with educational problems is desirable for every school system where the value of its potential service is commensurate with the cost

To set up such an organization as an independent medical unit is quite a different matter. To begin with, the vast majority of behavior and emotional problems par itoularly those of young children, are not in themselves potentially psychiatric and thus elaborate study and treatment by such a group is not only unnecessary but entails a cost in time and money which cannot be justified. On the other hand in many older children conduct and educational problems arise which require a detailed study and treatment that can only be given by such an organized group as the child guidance clinic.

The minor or less important guidance problems and particularly those of the younger children are distinctly pediatric problems. These should be handled in a routine way by the physician and the emphasis should be on their prevention. It is much easier to prevent a behavior problem than to correct it, and the vast majority may be easily foreseen by the physician who is alert and has this phase of child development in mind.

That more serious problems will arise however is just as true as the fact that serious health problems arise in the child who has received compotent medical super vision from the time of birth. These problems often call for services of the technically trained surgeon otologist or urologist, for example to make a correct diagnosis and to outline and carry out the required therapy. The child guidance clink has a similar function in its own particular field. To separate such an organization from the rest of the medical body however is to limit its usefulness and value. Coordination and cooperation with the medical group as a whole is the best way in which the child guidance clinic may develop its influence as well as fulfill its oppor runtites.

The pediatric clinics as a whole are rapidly recognizing the importance of a special group within their organization for the handling of difficult conduct problems. This is the logical and sound place for a child guidance clinic. Where such a situation or "set up" has been created the rapidity with which the pediatric

clinic has become psychiatrically minded is amazing. What is more important than the work of a child guidance clinic per se which can only look after a small fraction of the problem children and whose work is chiefly therapeutic, is the influence of such a clinic in the pediatric group. Thus situated its influence extends to medical student, house officer and graduate student. I is upon these individuals in the ultimate analysis that the prevention of behavior and conduct problems will depend



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Sobee is a soybean product consisting of 61 0% refined soybean flour, 19% olive oil, 9% arrowroot starch, 6% Dextri-Maltose, 4% dicalcium phosphate, and 1% sodium chloride. When Sobee is reliquefied with water and Dextri Maltose No 2 is added, the analysis in many respects approximates that of the usual cow's milk formula Supplemented with cod liver oil and orange juice, it will maintain infants over an extended period as the sole source of food. The flavor of Sobee has recently been improved, so that infants take the mixture readily and gain normally.

Levy and Finkelstein state



that 38 of 40 infants sensitive to milk proteins showed definite improvement when placed on a Sobee diet. Klein, Rowe, Clarke, and others report equally good results Hill, describing the treatment of 80 eczematous infants with Sobee, observes that results were remarkable in some instances severe eczema disappearing within a few days

#### CEMAC

A Diet Free from Cereal, Egg and Milh

Many children are sensitive not only to milk proteins but to those of eggs and cereals as well If the allergic infant is placed on a diet of Cemac, any or all of these proteins can be withdrawn without danger A mixture of beef cauliflower, tomatoes, carrots, spinach, cane sugar Dextri-Maltose, olive oil, cod liver oil, dicalcium phosphate, and sodium acid phosphate, Cemac is designed to supply all the nutritive requirements including vitamins C and D, for normal growth of infants Cooked, strained, and homogenized, Cemac is ready for immediate use after dilution with boiled water. It may be fed from

the nursing bottle or as a soup Like Sobee, its analysis is similar to that of the usual milk formula

Since 1925 Cohen and his associates at the Asthma, Hay Fever, and Allergy Foundation, Cleveland, have been feeding allergic children on this vegetable soup "Allergic infants" Cohen reports, 'thrive on this det. In the vast majority the allergic symptoms disappear



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### "For those who are

### UNDERWEIGHT"

AT THIS SEASON OF the year when bodily resistance is at its lowest ebb and so many patients—particularly little children—are underweight, it is well to remember that Maltine With Cod Liver Oil has been prescribed by physicians for more than 50 years to correct those very conditions. One physician\* writes us, "For those who are underweight I prescribe Maltine With Cod Liver Oil."

While the value of cod liver oil as an aid in building up resistance and weight is thoroughly recognized, it is a matter of concern to physicians that plain cod liver oil is not well tolerated by some infants and children Maltine With Cod

Liver Oil, on the other hand, is well tolerated and ensily assimilated by all ages

Containing, as it does, 70% Maltine—a concentrated liquid extract of the nourishing elements of malted barley, wheat and oats—good sources of vitamins B and G, and 30% pure, vitamintested cod liver oil of high potency in vitamins A and D, Miltine With Cod Liver Oil is not only rich in the four vitamins, but in other elements essential to health and growth

Maltine With Cod Liver Oil is biologically standardized and guaranteed to contain four vitamins—A, B, D and G When administered in either orange or tomato juice, vitamin C is added Biological report sent to physicians on request The Maltine Company, Est 1875, 30 Vesey Street, New York, N Y

Biological report sent to physicians of request The Maltine Company, Est 1875, 30 Vescy Street, New York, N Y

\*Name on request

THE ORIGINAL

WITH COD LIVER OIL

Introduced m 1875

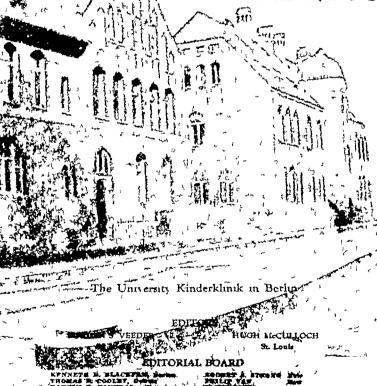
CERTIFOODS—served vegetables of known and guaranteed vitamin potency. Prepared by an exclusive process which conserves maximum vitamin values proteins calories and mineral salts—particularly iron and phosphorus. Prepared by Certifoods, Inc., subsidiary of The Maltine Company.



JULY 193

CZERNY FESTSCHRIFT

# THE JOURNAL OF PEDIATRICS



### "For those who are

### UNDERWEIGHT"

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Name on request

THE ORIGINAL

WITH COD LIVER OIL

Introduced in 1875

CERTIFOODS—served vegetables of I nown and guaranteed vitamin potency. Prepared by an exclusive process which conserves maximum vitamin values proteins calories and mineral salts—particularly iron and phorphorus. Prepared by Certifoods. Ive. subsidiary of The Maltine Company.

# THE JOURNAL OF PEDIATRICS



# Preventing NUTRITIONAL ANEMIA in Infants through a Normal DIETARY REGIMEN

NUTRITIONAL anemia was present in 45% of the breast-fed and 51% of the bottle-fed in a group of more than 1,000 infants studied by Mackay <sup>1</sup> Although this anemia was of mild degree, it was sufficient approximately to double the morbidity among the artificially fed

#### Anemia Prevalent

Commenting on this work, the British Advisory Committee on Nutrition writes,

This form of anaemia is prevalent among infants, especially those living under conditions of city life, and is attributed to a deficiency of available iron and possibly also of copper. Its most important feature is susceptibil-

"	IRON	COPPER
Cow's Milk, 14 oz.	I oI mg	0 166 mg
Dextri-Maltose with		
Vitamin B, 1 oz.	2.40	0 570
	3.41	0 736
Daily Requirement *	- •	"traces"
Dany Requirement	3 11	traces

It is generally agreed that breast milk and particularly cow's milk are markedly deficient in iron and copper But when 1 oz of Dextri-Maltose with Vitamin B is added to 14 oz cow's milk, properly diluted (as at 1 month), the above increase in iron and copper results

ity to infection, particularly a liability to colds, otorrhoea, bronchitis, and enteritis, and a tendency for infections to become chronic '2

Iron, incorporated in powdered milk, should be given as a routine to bottle-fed infants, according to the recommendations of this committee in a report to the Ministry of Health

Milk Deficient in Iron

Stored in the liver of the full-term infant is a supply of iron and copper theoretically sufficient for the first six months of life. But actually the reserve is subject to wide variation, probably because of variations in the iron content of the mother's diet during pregnancy. Hill, for example, says, If the mother is anemic herself, or if she has eaten little iron-containing food during the last months of pregnancy, her off-

	IRON	COPPER
Cow's Milk, 20 oz	1.44 mg	o 24 mg
Dextri-Maltose with		
Vitamin B, 1½ oz.	3 бо	o 855
Mead's Cereal (dry), 1/4 oz.	1 70	0 09
or Pablum	6 74	1 185
Daily Requirement*	4 18	"traces"

When 1/4 oz of Pablum is fed to the 3 months-old infant receiving 20 oz cow's milk and 11/2 oz Dextri Maltose with Vitamin B, a significant increase in iron and copper takes place.

spring is born with an insufficient iron deposit

The trend is also toward the introduction of iron-rich solid foods at an early age. The iron content of many foods is variable, however. Leichsenring and Flor' found that children's diets planned to contain 5 and 85 mg iron actually contained only 325 and 65 mg, respectively. Pablum, higher than most foods in iron and con-

taining standardized amounts of this mineral can be administered as early as the third month. Clinical studies by Summerfeldt<sup>5</sup> show that Mead's Cereal (of which Pablum is the pre-cooked form) is capable of increasing the hemoglobin percentage of growing children.

\* The desirable iron intake for children according to Rose et al is 0.76 mg per 100 calones.

Infant of 1 month (814 lb.) and infant of 3 months (1114 lb.) both require 50 calones per lb.\*

MEAD JOHNSON & COMPANY, EVANSVILLE, INDIANA, US A

MEASURE

PRESCRIBED AMOUNT INTO

CEREAL BOWL

ADD HOT WATER

AND

STIR WITH FORK

ADD

MILK OR CREAM

AND

Ferve



#### PARILIM

SUPPLIED IN 1 POUND CARTONS AT DEDG STORES

Pre-cooked Mead's Cereal Dried Ready to Serve

Consists of wheatmeal catmeal commeal wheat embryo yeast, alfalfa leaf and beef bone. Supplies vitantins A B E, and G and calcium phosphorus iron, copper and other essential minerals,



Sugar and Solt to Toste for Older Children and Adults

PABLUM is unique among cereals. For it is not only richer than any others in a wider variety of vita mins and minerals but it is the only pre-cooked cereal which is dry-packed yet which can be served hot.

To prepare Pablum for the infant, all the mother need do as measure the prescribed amount directly into the cereal bowl and add boiled hot water site ring with a fork. (Milk or water-and-milk of any temperature may be used for infants—cream for older children and adults.)

This case of preparation makes Pahlum especially welcome in families where the benefits of hot cereals are often denied simply because the process of cooking ordinary cereals is too long and too bother some. As it is a day cereal, Pablum keeps indefinitely and requires no refingeration. Being day only cereal is paid for not added water This fact plus the manner in which it is prepared makes Pablum "economical,"-no wasta.

Like Mead's Cereal, Pablum represents a great advance among cereals in that it is richer in minerals (principally celcium, phosphorus, iron, and copper) and vitamins (A, B, E, and G) it is baseforming, and it is non-irritating Added to these special features it is abundant in protein, fat, car bahydrates and calories.

Unlike many foods that are "good for growing children," Pablum tastes good.

## HAVE YOU SEEN Clapp's NEW **Enamel Purity Pack?**

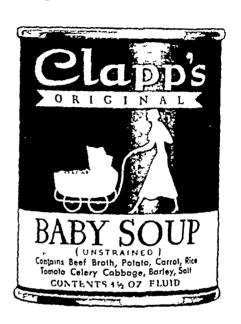
YLAPP'S Original Baby Soups and A Vegetables are now being sold all over the country in the new Enamel Purity Pack and sold at a new low price

These metal containers afford a special enameled protection against food acids They provide the purest packing that baby foods can receive!

America's largest variety of infant foods can now be purchased as cheaply as any other reputable brand in the field So if, in the past, you have wished to give your young charges Clapp quality but have hesitated because of a slightly higher price you can now freely advise these favorite foods

We want you to see and try Clapp's foods in their new packing Send in the coupon and receive them all-free.

> Clapp's original Baby Soups and Vegetables · · also packed in glass jars at former prices



### 15 VARIETIES

strained)

Baby Soup (Strained) Baby Soup (Un I egetable Soup Beef Broth Wheatheart Cereal Spinach



Carrots Peas Asparagus **Tomatoes** W ax Beets Prune Pulp Apricol Apple Sauce Pulp

HAROLD H. CLAPP, INC. Dept. J-4, 1328 University Ave. Rochester, N. Y.
Please send me free of charge a com plete assortment—15 varieties—of Clapp's Original Baby Soups and Vege tables in the new Enamel Punty Pack
Name
Address
City State Print name and address plainly

# Keep babies on cod-liver oil this summer!

\*



Most physicians now recognize the need for prescribing an anti-mehitic all year round, in summer as well as during the more inclement seasons. Comparatively few babes they find receive enough Vitamin D from sim shine even when the weather is warm.

There is the danger with very young babies of exposing them too long to the sun the risk with babies in large cities that other factors such as smole and soot may prevent them from receiving some of the sun's protective rays and the possibility that bad weather may make outdoor protection un certain and irregular

This is why it is desirable in summer to depend on some regular daily source of Vita min D Many doctors prescribe Squibb 10 D" Oil. Specially enriched with Viosterol it has ten times the Vitamin D potency of standard cod liver oil as defined by the

Wisconsin Alumni Research Foundation

Babies tolerate it easily. There is very little danger of digestive upset. One tea spoonful of cod liver oil supplies only about 40 calones.

In addition to Vitamin D Squibb Cod Liver Oil with Viosterol 10 D contains an abundance of Vitamin A, the factor which promotes growth and is an aid in building resistance. Many physicians favor giving babies plenty of Vitamin A in summer to help acquire good general resistance with which to meet infections

Every 100 grams of Squibb 10 D Oil contains not less than 70 000 U.S.P units of Vitamin A and 133,333 A.D M.A. (13,333 Steenbock) units of Vitamin D

Babies need these factors at any season Prescribe Squibb Cod Liver Oil with Viosterol 10 D for them routinely all summer

## SQUIBB COD-LIVER OIL with VIOSTER OL

Manufactured under license from the Wisconsin Alum

Research I undation and accepted by the Council on Pharmacy and Chemistry, A.

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FOUNDED 1876

#### Makers of Medicinal Products

## AMPOULES PHYSIOLOGICAL BUFFER SALTS

(Hartmann's Solution)

For the Treatment of Dehydration with Acidosis or Alkalosis

Supplied through the drug trade in 10 cc ampoules, No 261, and in 20 cc ampoules, No 262 each in boxes of six and twenty-five ampoules

## AMPOULES MOLAR SODIUM r-LACTATE

Prepared according to the method of Dr Alexis F Hartmann

For the Treatment of Severe Acidosis When Prompt Action
Is Necessary

Supplied through the drug trade in ampoules containing 40 cc, No 278, in boxes of a single ampoule, and in boxes containing six and twenty-five ampoules

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ADDRESS ELI LILLY AND COMPANY, INDIANAPOLIS, INDIANA, U S A



### VEGEX

#### for the B Vitamins $B_1 B_2$ or G

Vegex-How Made

Vegex comes from barley and corn slow grown brewers years.

After settling from the beer the hop resins are washed out, a consumer in the presence of the sail. The extract is filtered off, condensed and a mail amount of flavoring from such vegetables as tomato and celly a lifed and jumpled on chemical composition or vitamin B potency.

The finished condensed extract contains around 11 per cent of sodium chloride which figures less than a stram per teaspoonful in arranging dits. The iron, contained in the whole grain is gathered by the vessel and is particularly as imilable in legex.

#### Constant Feeding Tests for Vitamin B Strength



BOTH STARTED

2 GRAMS
B-VITAMINS
PAR PAY FACH CH DAYS -2The vitamin B potency of Vegex is checked constantly by feedling tests not only f r the unit required for recovery after depletion but the amount required for good normal growth successful reproduction and successful rearing. Prom 30 to 100 ms give recovery after depletion 200 ms; give normal growth, 400 to 600 ms give receveratel rearing of young On these standards Vegex ranks at the top

#### Early Use for Vitamin B

When Funk discovered the thing he named "Vist mine the Verex extract was found a potent, palat able and available food source was selected during the World War to prevent and relies berthert among the troops in Germany to add protein to the restricted food supply.

After the war Verex was early turned to in medit centers as a source of vitamin B. later of B or G. The pronounced value of Verex for stimular in the provent among both much may be the provent among both much and the provent among both much and related discolers has been hown.

It may stimulate finish or capricious appetites is of value in the liquid diets for no to-operative cases. It adds increased consumption of food is frequently a means for quick pick up in strength When Funk discovered the thing he named "Vita

#### In Anemias

Medical centers in India, Porto Rico England and the United States report the value of this vitamin B extract soil in England as Marmite and in United States as voxex in the treatment of permicious and related anemias. Wills (British Medical Journal Junco 70 1811) Vaughn and Hunter (The Lancet, Vpril 16, 1872) Goodall (The Lancet Oct. 8 1857) Strmuss and Casile (The Lancet, July 16 1912) Uneter (The Lancet, Oct. 17 183.) Recentir Wills Camb and Lond report in the Lancet (June 1 1833)

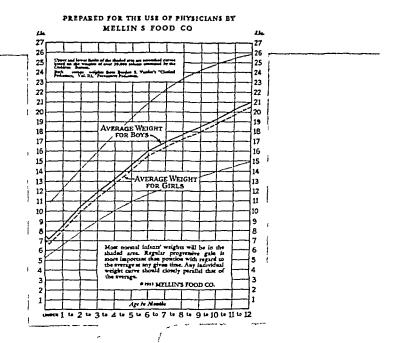
and Lond report in the Lancet (June 1" 1933)
I Chancal in I of most prip ration coatsi ing vitamins B B and Ba. [iled it above that my of these vitam as har hemospecitic properties in topocal macrocytic semi:
"2. Marmite (tepex the United States) as tolysed year product was set contractly I implied case.
Chart No I on this parse shows the shount of B vitamins necessary for successful returning as compared with the amount one-shall which give se good with the hen the mother a B t. La supplemental with the Nam B vitamins. To the vitaming C should have been added.

Sufficient samples for clinical use, and "VITAMINS," hick brings the sub-sect up to date together with special directions for the use of Vegex by physicians

VITAMIN FOOD CO, INC and VEGEX INCORPORATED 122 HUDSON STREET NEW YORK CITY

up in strength

I



## May We SEND YOU THIS NORMAL GROWTH CHART?

In keeping with our policy—no advertising or feeding formulas for the public—this new chart will be distributed upon request to physicians only.

MELLIN'S FOOD CO

•	
,	
No ADVERTISING	
,	
TO THE PRICE N.C.	_
ADVERTISTNG	

or feeding formulas

## EXPLOITATION of the MEDICAL PROFESSION

VERYWHERE it is rampant—newspapers, magazines, billboards, radio
'Your doctor will tell you that "' 'Medical science has found that
"The greatest specialists in Timbuctoo say that "' And the
rest of the story is, of course, "Use our pills or our vitamins three times
a day; ask your doctor"

You are forced to compete with those who offer your patients free ad vice regarding medical treatment. You deliver Mrs Blank's baby today, and tomorrow she will receive by mail samples of baby foods with complete directions how to use them Indeed, some physician representing a commercial organization and knowing that the case is in your hands may address a personal letter to your patient offering his services free

It has been said that ten more years of the present trend of interference in medical practice will do away with the need for private practice of infant feeding and other branches of medicine

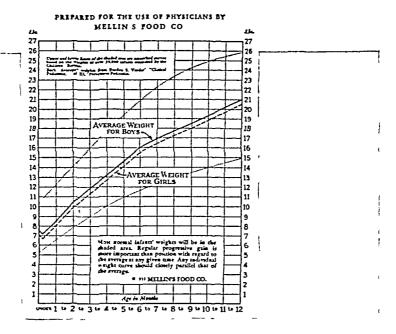
Mead Johnson & Company have always believed that the feeding and care of babies and growing children is an individual problem that can best be controlled by the individual physician. For over twenty years and in dozens of ethical ways we have given practical effect to this creed. We hold the interest of the medical profession higher than our own, for we too, no doubt, could sell more of our products were we to advertise them directly to the public.

So long as medical men tacitly encourage the present trend, so long will serious inroads continue to be made into private medical practice. When more physicians specify MEADS Products\* when indicated, more babies will be fed by physicians because Mead Johnson & Company earnestly cooperate with the medical profession along strictly ethical lines and never exploit the medical profession.

Dextri Maltose Nos 1, 2 and 3; Dextri Maltose with Vitamin B; Yead's Viosterol in Oil 250 D; Nead's 10 D Cod Liver Oil; Mead's Newfoundland Cod Liver Oil; Mead's Powers Yeast Powder Mead's Brewers Yeast Powder Mead's Brewers Yeast Tablets Wead's Powdered Lactic Acid Nilk Nos 1 and 2; Yead's Powdered Whole Milk Alacta; Mead's Powdered Protein Milk Casec Recolac Sobee; Mead's Viosterol in Halibut Liver Oil 250 D; Mead's Undiluted Halibut Liver Oil



"We Gire Keeping the Faith"



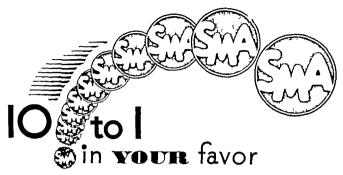
## May We send you this normal GROWTH CHART?

In keeping with our policy—no advertising or feeding formulas for the public—this new chart will be distributed upon request to physicians only.

MELLIN'S FOOD CO

Boston, Mass

	1
1	No
	ADVERTISING
	or feeding formulas
	for the public.



HEN you prescribe S.M.A. for a normal infant deprived of breast milk you do so with the assur ance that the chances are 10 to 1 that the child will do unusually well on it.

S.M.A. produces excellent nutritional results in most cases and produces these results more simply and more quickly and there is a wealth of clinical evidence to back that claim

#### Physicians Report Results

As one example of this, take the following answers to a questionnaire sent to a representative group of physicians early in our work:

- Q.—Havetbeaverageresults Q.—Has the feeding with obtained by you in fred ing S.M.A. been excellent good fair or boor?
  - A -Excellent 74 2% Good 25 8% Fair 0% Poor 0%
- Q.—Do you feel their S.M.A. is of selecto yes in year practice from the stand point of preventing nu-trational diseases?
  - A -Yes 97 1% Undecided 2.9%

- S.M.A. been easier and less annoying than with other foods or mixtures used by you beretofore?
- 4 —Yes 1007 Q.—Have your nutritional results been better than with other foods a mix tures used by you beretelore?
  - Λ \ a 83% No 14 6% Undecaded 2.4%

If you are interested in saving yourself exact ing detail in infant feeding, and want to be assured of excellent results in most cases you can do no better than prescribe S.M A., the formula prepar ed with laboratory exactness for infants deprived of breast milk.

#### SMA Ahead in 1915 Still For Ahead

S.M.A. has been antirachitic from its beginning in 1915 S M. A. was a revolutionary departure then, was far ahead in 1921 when it was offered to the profession generally and is still far ahead in numerous unhersided ways some of which are:

- 1. Buffer value is practically identical with bresst milk
- 2 Fat has the same Reichert Meissl number Iodine number Polenske number Saponifi cation number melting point and refractive index as breast milk fat
- 3 The pH is the same as breast milk.
- 4 Electrical conductivity is the same as breast milk.
- 5 Freezing point is the same as breast milk. 6. Osmotic pressure is the same as breast milk.
- 7 Curds produced by the action of the gastric juices on S M.A. are soft and practically the same as breast milk.
- 8. Stools are acid and also physically similar to those of breast fed infants.

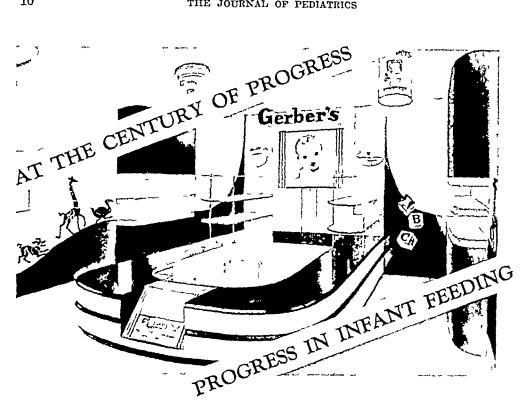
#### Is The Only Antirachitic Breast Milk Adaptation



S.B.A. is a food for infects—derived from tuberculin tested cour! with, the fat of which is replaced by animal and vegetable fats including biologically tested cod I ver oil; with compaire sy assume arms regresses ant recursing nonequestly tested cod l our oll, with the addition of mills trap potentism, to theiride and sells; altractive forming an article receiving the districtions, it is exertially smiller to be much mills in percentages of protein, fet carbobydrates and ash in chemical constants of the fet and he physical properties.



Try S.M A. in your own practice. For samples samply strach this para graph to your letterhead. S. M. A. Corporation, 4614 Prospect Ave., Cleveland, O. 56-73



THE many professional requests for samples of Gerber's Strained Foods are indicative of the physician's interest in the commercial developments required to keep pace with medical progress in infant feeding

The Gerber Products Company welcomes and invites this continued interest. May we urge you cordially to visit the Gerber Exhibit at the Century of Progress Exposition and learn at first hand about the Gerber Strained Products for Baby?

Mr R W Decker and Mr Walter Fleming who have specialized on Gerber detailwork with physicians will be in charge of the exhibit

They will be assisted by Miss Harriet E Davis R N-for the past 9 years Director of the College of Nursing at Indiana State University and just recently associated with the Gerber Department of

Nutrition directed by Lillian B Storms, Ph D

Miss Davis is particularly well qualified thru her professional work and training to impress on lay visitors the importance of relying only on a physician's advice on all questions connected with infant feeding This Gerber policy of active co-operation with the medical fraternity maintained in all Gerber advertising will be followed rigidly in lay contacts at the Century of Progress

The Gerber Exhibit is located in the Hallof Science Fountain Rotunda Century of Progress Exposition You are invited to use its convenient location as a

meeting place

GERBER PRODUCTS COMPANY Fremont, Michigan

(In Canada Fine Foods of Canada Ltd Windsor Ont)

STRAINED Tomatoes—Green Beans—Beets—Vegetable Soup— Carrots—Prunes—Peas—Spinach, 41/2 oz. cans.

STRAINED Cereal, 101/4 oz. cans 15c at Grocers and Drugglits

9 STRAINED FOODS FOR BABY

#### A Worthy Companion Product to S M. A.



## PROTEIN S.M.A.

(ACIDULATED)

	Anai	YSIS*	
Protein	35%	Ash	0.6%
Fat	2.2%	рH	46
Carbohydrate	2.8%	Calories per ounce	e 15
Calorie	s per 100 c	i.c. 10	
* When di	wied acc	ording to directs	

**5 M A.** is for normal infants Protein S.M.A. (Acidulated) was developed to suit certain devia tions from normal. It has been used by physicians for years with satisfactory results.

#### Uses of Protein S M A. (Addulated)

- For the correction of diarrhea malnutrition and marasmus
- For prematures and other infants requiring a high protein intake
- May be used either as a protein milk or as a large acid milk.

#### Characteristics of Protein S M A. (Acidulated)

A cultured lactic acid food for prematures and other infants requiring a high protein intake for the correction of diarrhea, malnutrition and mar asmus derived from tuberculin tested cows milk the fat of which is replaced by animal and vege table fats including biologically tested cod liver oil with the addition of lemon juice, casein poiss-sum chloride and salts altogether forming an antirachitic and antirorbutic food

#### How to Correct Diarrhea

After a starvation period of twelve to twenty four hours on boiled water or gelatin water of younce of gelatin to one pint of boiled water) the infant should be given according to the following schedule Protein S. M. A. (Addulated) prepared in proportion of four level tablespoont to nine ounces of water in Day 2nd Day 3nd Da

Severe cases 3 oz. 6 oz. 9 oz. Medium cates 10 oz. 15 oz. 20 oz. Mild cases 15 oz. 30 oz.

The shore quantities are to be increased until the proper amount for the patient's age and condition is reached, which is 200 c.c. per kilo of body weight per twenty four hours, or three ounces per pound of body weight per twenty four hours. However the total twenty four hour intake need not go above thirty two to thirty five ounces or 960 to 1030 c.c.

After 48 hours, or sooner if the distribes has stopped, ALERDEX (Protein Free Maltore and Dextrins) should be added gradually beginning with one ounce to the quart, and increasing until the infant is gaining steadily in weight. In certain cases it may be necessary to increase the carbohydrate to a total of 12 to 15% (3 to 4 ounces of carbohydrate to the quant-

SEND FOR LITERATURE

Simply attach this paragraph to professional card or letterhead for literature on Profess S. M. A. (Acidulated). 56-73



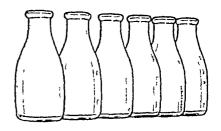
S M A. CORPORATION CLEVELAND OHIO -ATTENTION IS CALLED TO THIS NEW POURING SPOUT



# ONE inexpensive can of KARO SYRUP effectively

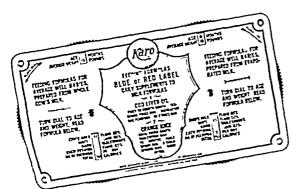
## modifies SIX quarts of whole milk

On the basis of tested and ap proved feeding schedules averaged for babies up to an age of nine months, one tablespoon of Karo would be used with about 6 fluid ounces of milk On this basis, a one and one half pound tin of Karo (which sells in grocery stores for about 12¢) will furnish the necessary amounts of easily assimilated carbohydrates, dextrin, maltose and dextrose, for 6 quarts of whole milk Probably no other infant food of equal acceptance is available at such low cost as Karo



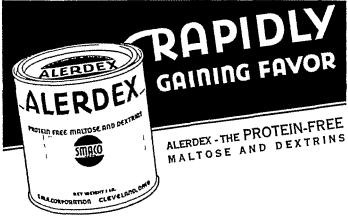
Feeding schedules, are not supplied to the laity Mothers are always advised to consult a physician in regard to the nutritive requirements of the infant.

Use of the pouring spout (furnished without charge) is recommended. This spout insures clean-liness—lessens danger of contamination—prevents waste.



#### FREE TO PHYSICIANS

This convenient calculator of feeding schedules is accurate, in structive and helpful Themakers of Karo will gladly send one to you on receipt of your name and address Write to Corn Products Refining Company, 17 Battery Place, New York City



#### WHY IS ALERDEX PROTEIN-FREE?

• Since certain proteins are frequently the cause of eczemas and other forms of allergy, it is desirable to eliminate these offending proteins from the infant diet. Cereal proteins are frequently present as contaminants in some milk modifiers. The routine use of a protein free carbohydrate in all milk modifications should help to diminish the incidence of these troublesome eczemas. Alerdex is a protein free carbohydrate developed by our Research Division to meet this need and the demand for it is steadily increasing.

A modest announcement of Alerdex a year ago found physicians ready and anxious for such a product. There is now a definite trend to use Alerdex routinely in all milk formulas.

Of course Alerdex should always be used as the carbohydrate addition with Smaco Hypo Allergic Milks with the assurance that eczemas due to cereal protein sensitization will not be aggravated

#### CHARACTERISTICS OF ALERDEX

- I Helps prevent eczemas when used routinely due to absence of offending protein.
- 2 Use present fermulas because Alerdex has same caloric value and percentage of maltose and dextrina.
- 3 Dees not cake on exposure to air because it is non hygroscopic.
- 4. Disselves readily in warm water or milk.
- 5 Snew white, free flowing powder
- inexpensive—in spite of extra processing under technical control, costs no more
- O 1965, E.M.A. Corporation, Cloryback, Ohlo

#### APPROXIMATE ANALYSIS OF ALERDEX

Alterdez le essentially a mixture of approximat ly equal paris of maltese and destrine. It is prepared by a new thermally-controlled process of the ensymble hydrolyals of non cereal starch, as a result of which it contains no protein contaminant.

Moleture	38
Ash	0.5
Fat (ether extract)	0.0
Hydrolysed protein (N x 6.25)	0.5
Reducing sugars as maltese	50.6
Dextrine(by difference)	45.0
Level tablespoons, per ounce	4
Calories per level tablespoon	27%
Caleries, per ounce	110



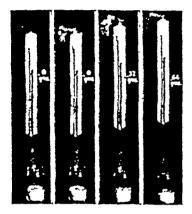
Prescribe Alerdex in your own practice For samples and literature simply attach this paragraph to your letterhead or prescriptien blank. B.M. A Corperation, 4414 Prospect Avenue, Cleveland Ohio 55-7

## CURD TENSION

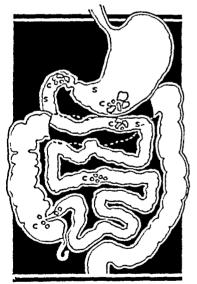
- AND INFANT, FEEDING -

ITS . EFFECT . UPON . THE . ASSIMILATION . OF

#### **PROTEINS**



BREAST SIMILAC POWDERED COW S MILK



C-Cows milk S-Similac Fehernatic drawing of the relative size of the curds of cows milk and Similac vom thed by six weeks old pupples after onehalf bours ingestion.

THE most available and the most easily digestible form of protein for infants is the protein of milk. The protein of breast milk is more digestible than that of cow's milk.

"In the light of our present knowledge, the chief cause of the difference in the digestibility of the protein of human milk and that of cows milk lies in the greater proportion of casein in cows milk."

"It is the formation of large curds which renders the casein of cows milk so much more difficult of digestion by the infant than that of human milk. If the formation of large casein curds in the stomach can be prevented, the casein of cow's milk is easily digested."

In SIMILAC the large easein curds are not formed The curds formed when the gastric enzymes act upon SIMILAC are small and flocculent, registering zero on the tensiometer, as shown in the illustration, hence more easily digested

The finer the curd the greater the surface area. The greater the surface area the more exposed are the fats, carbohydrates, proteins and salts to the digestive enzymes. Result——a more complete utilization of the food elements

<sup>1</sup>Morse and Talbott Diseases of Nutrition and Infant Feed ing. pgs 214, 215

Samples and literature will be sent on receipt of your prescription blank

SIMILAC-Made from fresh skim milk (casein modified) with added lacture talts milk fut and vegetable and cod liver oils

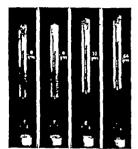


M&R

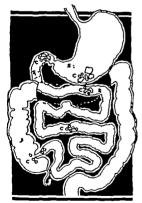
## CURD TENSION - AND INFANT FEEDING -

ITS EFFECT UPON THE ASSIMILATION OF

#### SALTS



BREAST SIMILAC POWDERED COW'S MILK MILK



C.—Cow ralls S.—Similae Schematic drawing of the relative size of the cards of cow's milk and Similae vouted by six weeks old pupples after onehalf hour ingustion.

HE mineral salts play a very complicated part in digestion because they are not only absorbed by the in testines but also may be re-excreted into the digest ive causl."

"The mineral salts are of even greater importance in infancy than in later life because of the rapid growth of the hony structure. The salts are also necessary for cell growth and are important constituents of the blood and digestive juices, facilitating secretion, absorption and excretion."

Some of the important mineral salts are encased within the large tough curds formed from cow's milk, and only those salts that are not encased in the curds are available for metabolism.

The curds formed from SIMILAC are small and flocculent, registering zero on the tensiometer as shown in illustration hence the mineral salts of SIMILAC are available for meta holium.

The salts of the cows milk used in the preparation of SIMILAC are rearranged, particularly with reference to cal cium, sodium, and potassium, as well as phosphorus and chlorine SIMILAC has a selt balance that cannot be obtained in the ordinary milk dilutions or modifications as made in the home or laboratory

The finer the curd the greater the surface area. The greater the surface area the more exposed are the fats carbohydrates, proteins and salts to the digestive enzymes. Result a more complete utilization of the food elements.

More and T thet Diseases of Notrities and Infant Feeding, pg. 59
 M relett Infant Natritien, pg. 43

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SIMILAC-Made from fresh skim milk (caseln medified); with added lactors, salts, milk fat and epstable and cod liver edle.



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LABORATORIES. INC.,

## Effective LAXATIVE

## MEDICATION

Sodium Glycocholate 1/4	gr
Sodium Taurocholate 1/4	gr
Phenolphthalein1/2	gr
Extract Cascara 1/2	gr
Aloin1/8	

TABLETS

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Oxiphen Tablets are particularly useful in habitual constipation because they produce gentle, yet effective laxative action throughout the intestinal tract, stimulating activity of both the secretory organs and the intestinal musculature. They may be used over extended periods without losing their



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The Ouphen formula combines the hepatic stimulant and chologogue action of the bile salts ("the only reliable chologogue known"—Cushny) with the tonic lavative effect of cascara, the simple lavative action of phenolphthalein and the stimulant action of aloin on the colon Kindly use the coupon for literature and clinical sample

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(	City State

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with

bridge table variations



"Be sure to use

Feeding Formula for One Day

"My mother always says



"Try\_\_\_\_Brand Its such a prelity name for a milk, isn t it?



MUCH free advice on infant feeding can be obtained across the bridge table. But should a mother rely upon this kind of advice to guide her in her choice of Evaporated Milk for baby?

When you prescribe Evaporated Milk for infant feeding, you have in mind a milk with certain qualities wholesomeness, freshness and purity But the bridge table authorities may not know which brand of milk measures up to your high standards.

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The Borden Company produces Evapora ted Milks in which the physician will find the quality he demands for infant feeding. Careful selection of raw milk and rigid safeguards throughout manufacture guarantee the quality of every Borden brand...Borden s Evaporated Milk Pearl Maricopa Oregon St. Charles Silver Cow All are accepted by the American Medical Association

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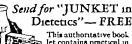


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- -nursing mothers
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The nutritive values of milk are fully retained in junket. Digests easily because the enzyme rennin performs the first step in digestion of milk Junket provides attractive variety in all milk diets.

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lag flavors, awartened, in
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#### HIGH GRADE MILK

Only pure cow's milk from tuberculin-tested herds is used Milk extremely low in bacteria count—abso lutely fresh Lactogen is free from pathogenic germs



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Because the milk used is so fresh, pure and free from contamination, complete safety is assured by mild processing, at no time more severe than the regular pasteurization.

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White regarded by the medical profession as a valuable intestinal lubricant, mineral oil has certain disagreeable features—notably the tend ency to rectal leakage—which limits its use.

More than a year ago tests were begun in the Maltine research laboratories to evolve an effective emulsion which would retain the advantages of the mineral oil and at the same time eliminate the objectionable features. MALTINE WITH MINERAL OIL and Cascara Sarrola with creative

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This mineral oil is incorporated with the Maltine by a special vacuum process by which the mineral oil is broken up into very minute particles. Laboratory and clinical tests covering a period of many months have shown that this combination is superior to the plain mineral oil in taste and appearance. The tests also indicate that the new emulson lessens the tendency to leakage because of the finely divided nature of the oil present and the small dosage required

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Physicians may satisfy themselves of the therapeutic value of this new mineral oil product by sending in the attached coupon

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SEE MALTINE ADVT ON BACK COVER

When Babies are suffering from Diarrhea, Vomiting—Summer-Complaint caused by Hot Weather or Improper Feeding they require

## INDIVIDUAL FLEXIBLE FORMULAE

#### to meet their needs

THIS can be accomplished only through a flexible food—one which will allow of a change in the percentages of its component parts—protein, fat, carbohydrate and water

Diarrhea and vomiting both cause a loss of water to the system and dehydration is, without question, the most serious result of summer-complaint

Babies cannot stand prolonged starvation. It is not how much they ingest, but how much they are able to digest and assimilate that determines the choice of food. "One of the great advantages of milk powders is the possibility of varying the relation between water, fat and other elements of the milk." (Porcher)

Dryco is the food of choice since it requires no refrigeration, is always fresh and ready for use, may be given in all degrees of concentrations and modifications—thereby allowing easy regulation of the quantity of water to be ingested for a given amount of protein, fat and carbohydrate

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#### MALNUTRITION

search Foundation)

#### -especially in children who dislike milk

William malnutrition in children may be due to premature both to some constitutional debility or the development of some serious disease, the great majority of cases are due to improper or faulty diet

Insufficient milk is by far the most serious failing in children a diets. This is due no doubt, to the fact that so many youngsters dislike milk and refuse to drink it. More and more physicians are meeting this problem by prescribing Cocomalt—which is as alluring as chocolate soda to child ren



Cocomalt! accepted by the C mailtee on Food of the Ameriean Medical Association. That is your best of it value as a food

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Prepared as directed, Cocomalt adds 110 extra calonies to a cup or glass of milk—increasing

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This rich Vitamin D content, combined with

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At grocery and drug stores in 14-lb and 1 lb

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Cocumalt is a scientific food concentrate of relocted cocoa, sucrose, skim milk, barley mult extract, fiavoring and added Vitamin D

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Which should be replaced to avoid losses?

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#### use this LACTIC ACID MILK

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In the treatment of digestive disturbances of infants and for the premature or athreptic infant. Merrell-Soule Powdered Whole Lactic Acid Milk (Cultured) offers these very practical advantages.

It is easily digested—Approximates breast milk in digestive qualities—the spray process of drying breaks up the fat and proteins into fine particles which combine readily with the gastric inites

Its correct acidity promotes the assimilation of calcium

It is untritions—Contains all the vitamins and nutritive proper ties of grade A pasteurized milk. It is more palatable—The process of culturing results in a pleasing flavor—no sharp and bitter taste.

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It is economical and easy to use— Reliquefied by mixing in the proportion of one packed level tablespoon of the powder to two ounces of warm water—then stirred into complete solution

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# MERRELL-SOULE POWDERED WHOLE LACTIC ACID MILK

(CULTURED)



# Maintenance of a Healthy Mouth---

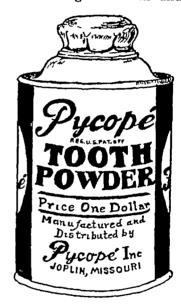
Surely is necessary to further the results of your efforts

Pycope Tooth Powder is beneficial in cleaning the teeth and

Pycope Tooth Brushes, when used correctly, provide the gum massage essential to mouth health

Pycopé Tooth Powder contains Sodium Chloride, Sodium Perborate, and Sodium Bicarbonate, plus flavoring oils—It has been accepted by the Council on Dental Therapeutics of the American Dental Association

Pycope Tooth Brushes are small and correctly designed to clean between the teeth. The junior size brush is adaptable for use by children up to the age of twelve





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These pathological conditions which depend upon epithelial failure may be expected to be improved by the oral administration of Caritol [solution of carotene—primary vitamin A—in vegetable oil] because of its ability to produce healthy epithelial tissue,

Carotene for Latent Deficiencies 'Until recently the versatility of vitamin A has apparently not been appreciated A remarkably increasing literature in the last year of two attests its growing importance in the chemistry of food and numtion, not only in the prevention and cure of certain ailments of man but, when supplied in liberal proportion in the maintenance of a satisfactory state of nutrition and high degree of health and vigor both in the growing child and in the adult. Ensierman & Wilber, J. A.M. A 98.2034 32

### Carotene Available in Three Products

I Smaco Caritol — A solution of carocene (primary vitamia A) in vegruble oil containing one milligram of carotene in each ten drops. Caritol may be prescribed alone or with other vitamia supplements (fish liter oils do and contain carotene). It is non-toxic, has no fishy taste and is prescribed in five to ten-drop dosages. Caritol is recommended for the majoremance of intact, healthy epithelial membranes. Product No. 309

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References Available—A digest of the literature dealing with carotene and vitamin A deficiency diseases, reprinted from American Medical Journals, available to physicians on request. 73 references are included.



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(Primary Vitamin A)

Catorece pigment of many rescribles research a many rescribles research a many requirement also hecessary for synthesis secondary numin. Ab Ilver. Carotene cognic compound, isolated 1826 formerly rate expensive now available in Cartole research for the contraction of the contrac

Carotene adopted by League of Nations Commission as provisional standard for biological measurement vitamin A potency pure Carotene has 3000 times the vitamin A potency of standard potent cod liver oil as defined by A. M. A.





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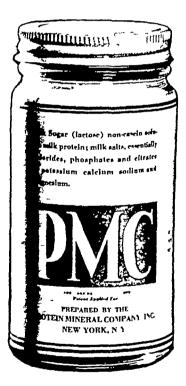
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PMC offers the pediatrician, for the first time, a means of supplying complete milk mineral rations in concentrated and palatable form Because it is derived from the serum or whey fraction of milk, PMC is immediately and fully assimilable. It can be given in milk or other beverages, or sprinkled over cereals

Because of its highly assimilable calcium, PMC is indicated in malnutrition, convalescence, to aid in the development of bones and teeth, and in the tuberculosis diet

It contains milk sugar (lactose), noncasein soluble milk protein, milk mineral salts, essential chlorides, phosphates and citrates of potassium, calcium, sodium and magnesium





Visit our exhibit at the A M A Convention Booth 30 Taste this unique product Hear its history and development Meanwhile you are cordially invited to use the coupon for a trial supply

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Please send me literature and trial jar of PMC.

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# Evaporated Milk is good milk for babies



The average normal baby is able to assimilate unsweetened evaporated milk as well as or better than bottled cow's milk (pasteurized or boiled) during the early months of life when milk constitutes the sole food Similar good results were obtained in the premature infants"—Kositza, Lillian Journal of Pediatrics, October, 1932

# Carnation Milk is good evaporated milk

Carnation Milk has come to be the evaporated milk of choice with many pediatricians because of its uniform high quality Scientific control of processing maintains this uniformity, which the physician finds a valuable aid in the construction of feeding formulas upon which he can depend to produce consistent results





Send for A Successful Infant Food written for physicians by a pediatrician of wide expensence Address Carnation Company 805 Mll watkee Gas Laght Bldg Milwaukee, Wis, 906 Stuart Bldg Seattle Wash.; or Aylmer Ont



From Entented Corus

# TRAINING THE BABY!

Dear Doctor

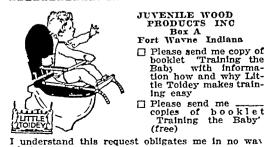
You no doubt know about Little Toidey has been one of the important factors in helping the mother follow the suggestion of the pediatricians to train baby early

When we developed Little Toidey in 1924, most mothers were waiting to "break" their babies long after the time when they are now completely trained. It has been our pleasure to work with the doctors in acquainting the mothers with the value of early training, and to provide them with that which helps in early training. Little Toidey

During these nine years since Little Toidey was first introduced, we have been privileged to meet many leading pediatricians. At the convention of the American Academy of Pediatrics in Chicago last month, we were happy to hear from almost every doctor who visited our display, an expression of acquaintance and appreciation of this great help toward easy early training and that regularity of functioning so necessary to health

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Yours very truly, JUVENILE WOOD PRODUCTS, Gestrude A.Thu



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- Dlease send me copies of booklet
  Training the Baby (free)
- whatsoever

## LITTLE TOIDEY

Makes Training Easyl



'You suggest early training there any reason aside from sanitation con consider Little Toldey important from a health standpoint why health standpoint

Perhaps your patients are asking similar questions. The answer is found in the booklet "Training the Baby which tells also all about Little Toldey with Foot Rest, Toldey One-Step and Two-Steps and other aids for baby's training and safety during the infant and toddler period

Our research has been extensive Mary K Muller our vice president BS MS Co-Muller our vice president BS MS Co-lumbia University has received the interest and suggestions of lending pediatricians and child psychologists throughout the United States and Canada. Every effort has been made to develop all our buby sids in hurmony with the best thought from this child health world

JUVENILE WOOD PRODUCTS, Inc. Gertrude A Muller, Pres, Mary K. Muller, V P Fort Wayne, Indiana Box A

## Mothers need help to end this daily

struggle . . . . Why not suggest a diet supplement?

Lack of Vitamin B may be impairing the child's appetite

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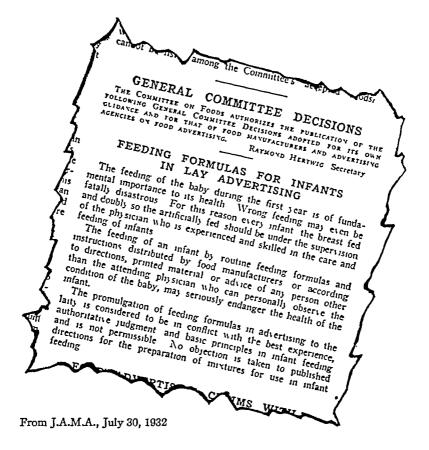
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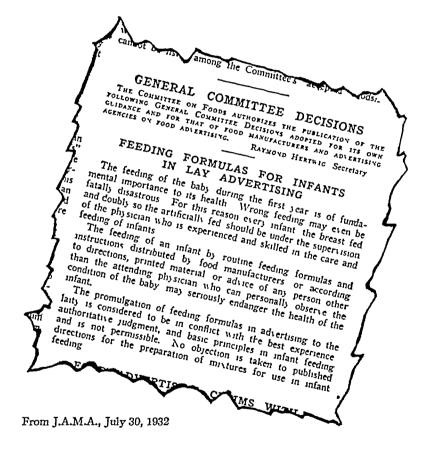


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## FESTSCHRIFT

## m honor of

## ADALBERT CZERNY

## on the occasion of his 70th birthday

## The Journal of Pediatrics

Vol III

July, 1933

No 1

Official Organ for
THE AMERICAN ACADEMY OF PEDIATRICS

EDITORS.

BORDEN S VEEDER St. Louis HUGH McCULLOCH

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## The Journal of Pediatrics

Vol. III

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### ADALBERT CZERNY-AN APPRECIATION

THE publication of this Festschrift by an American journal of pediatrics is evidence of the high esteem in which Adalbert Czerny is held and the appreciation that American pediatrics has for his contributions to the care of the sick and of the well child. To some of us who had the privilege of working with Professor Czerny during the Breslau days, it seemed inevitable that he should be chosen to fill more important positions as they became available

Graduating from the German University of Prague in 1888, he became a privat dozent in Professor Epstein's Chine in Prague in 1893 and in the following year was called to Breslau as Professor of Pedia tries to succeed Doctor Soltmann. In a remodelled flat, the polyclinic was opened in 1894 and shortly afterward an adjacent building was remodelled and served as a clinic for several years. In 1901 the new clinic was opened and in its arrangement Professor Czerny emphasized for the first time the value and importance of carefully observed dispensary material for the development of the hospital and its importance for the instruction of students and practitioners.

Some very interesting studies resulted from the careful observations made in this polyclinic. The clinic, with its convenient laboratory and library, was a place in which it was a pleasure to work. The daily rounds at 12 o clock frequently lasted until late into the afternoon as a particular case of interest was discussed in great detail in the master full manner of the Professor. It was quite an international family that gathered together at the Kinderklinik and I recall many interesting and happy days there. In 1910 Professor Czerny was called to Strassburg to take over the newly built Children's Clinic. It was during his first year in Strassburg that Doctor John Howland spent many months working in his clinic and derived much inspiration for the development of the pediatric clinic at Johns Hopkins. The Strassburg Clinic was a wonderful complex of buildings that Czerny was to leave after three years to accept the foremost pediatric chair in Germany which was

vacated by Professor Heubner in 1913. At the old Charite Kinderklinik, the chair of pediatrics occupied in succession by Professors Henoch, Huebner and Czerny is to the German pediatrician the highest honor that can be achieved. Although handicapped by old buildings and with insufficient tunds to rebuild after the World War, the wealth of material and the intensity of work made the clinic a Mecca for graduate students. Having had the opportunity to visit Czerny's clinics in all three cities, I could not help but appreciate how fortunate I had been to have spent my student days with him in Breslau where, in a small group, an intimacy existed impossible at the larger-clinics. Profoundly independent in all of his ideas, he combined the rare abilities of a great clinician, of an ardent teacher, and of a keen research worker. Professor Czerny is an excellent musician and plays the cello unusually well. The musical evenings in his home are a most delightful memory. His hobby is photography

Professor Czerny's contributions show his manifold interests. His early work on sleep, on amyloidosis and on blood volume are a prelude to his greatest contributions namely, his work on the gastro intestinal diseases of infancy. His first publication was with Moser, appearing in 1894, from Epstein's Clinic in Prague. His interest did not restrict itself to the diseases of the gastrointestinal tract but grew until it encompassed the nutrition of the normal infant and child in all its phases, as well as a comprehensive study of the nutritional disturbances of childhood. The culmination of his work and that of his many students, together with a complete study of the subjects, is the monumental work written with Keller, "Des Kindes Ernahrung und Ernahrungsstorungen und Ernahrungstherapie." The first edition appeared in 1906 and the following year, and a second edition in 1925-1927. To the student of child nutrition this work is a bible

There is another book to which I want to refer because it represents Czerny at his best. At a time when a very few were thinking of the relation of the pediatrician to the education of normal and difficult children, Czerny published his little book "Der Artzt als Erzieher des Kindes" This anticipated by many years our efforts to treat the be havior disturbances of children. Appearing in 1908, it has gone through seven editions and is as useful today as it was when first published

In conclusion, let me state again that in honoring Professor Czerny on his seventieth brithday we are but repaying a debt that American pediatricians owe to him and to many others in Germany. At a time when pediatrics in America was still in its swaddling clothes German masters took us into their clinics as students and by their inspiration and training played a part in the development of pediatries in America of which they may well feel proud

#### ERYTHROBLASTOSIS IN ICTERUS GRAVIS NEONATORUM

## ARTHUR F ABT, M D CHICAGO, ILI INOIS

#### INTRODUCTION

RLAT advances have been made in the past few years in our knowledge of the growth and development of the hematopoietic system. One of the greatest gaps in our knowledge of the physiology of hematopoiesis concerns the vital changes which take place just preceding and following birth. The differences in habitat between the intrauterine surroundings of the fetus, and the extrauterine en vironment of the infant, require different physical and chemical physiologic responses from fetus and infant, as has been shown by Czerny. The intrauterine and extrauterine physiology of respiration and circulation are probably better understood than the corresponding physiology of the hematopoietic system.

The embryology and development of the hematopoietic system is fairly definitely known and extramedullary blood formation is a fetal characteristic. The embryonic blood contains some elements (primitive erythrocytes) which are not encountered in the extrauter me circulation. There is still insufficient knowledge as to the fetal deposition of iron in the organs of the body. Bunge's theory of an iron reservoir or depot, laid down in the liver in the last few months of fetal life, which has so long been an accepted explanation is no longer held.

Following the onset of labor a gradual and continuous destruction of the erythrocytes of the polycythemic fetal blood occurs for a varying period. The exact site of this blood destruction is thought to be in the cells of the reticuloendothelial system and also to occur directly in the blood stream. Certainly according to Mann and his coworkers<sup>10</sup> the conversion of hemoglobin into bibrubin, does not occur in the liver cells. Physiologic returns a conatorum is closely linked with this destruction of the polycythemic blood of the newborn.

Under the title leterus gravis neonatorum a group of cases re ported in the literature have been segregated into a definite clinical syndrome. Newborn infants either at birth or a few hours thereafter develop a rapidly depening jaundice associated with anemia and the presence of a great number of immature red blood cells, crythro blasts in the circulation. Associated with the jaundice, anemia and crythroblastic blood picture are. Kern leterus iron deposition in

the internal organs, extensive extramedullary foci of blood formation, familial history, sometimes enlargement of the placenta and yellow coloring of the vermix caseosa, and infrequently a slight edema

An elucidation of the etiology of this disease of the newborn, would no doubt throw great light upon the physiology of hematopoiesis in the newborn and upon the mechanism of physiologic icterus neonatorum. Some very recent reports have suggested the association of familial icterus gravis with other diseases of the newborn. They may be grouped as follows.

(A) Icterus gravis neonatorum has been closely linked with hydrops congenitus universalis <sup>2</sup> <sup>11</sup> (B) Most recently it has been suggested that the clinical entity termed "anemia of the newborn" may show characteristics relating it to both reterus gravis neonatorum and hydrops congenitus <sup>10</sup> <sup>11</sup> <sup>12</sup> <sup>41</sup> <sup>48</sup> (C) Since the comprehensive review by Knoepfelmacher<sup>13</sup> in 1910, infection has been suggested as the etiologic agent, causative of reterus gravis neonatorum, and two recent reports suggest such an etiology <sup>14</sup> <sup>15</sup> I wish to add two cases of reterus gravis neonatorum with erythroblastosis to those already reported and to present a speculative discussion on the pathologic relationships of this clinical group

#### CASE REPORTS

CASE I.—Clinical History—A white male infant, weighing 4015 gm., was born on July 21, 1928. The mother had been well during pregnance, a para 11, the first born, a male, four years of age, was living and well. The mother's Wassermann reaction was negative, and there was no history of miscarriages, or stillbirths

At birth it was noted that the cry was feeble, respirations rapid, and the skin cold, and pale, with a slight yellow tinge. Jaundee developed a few hours after birth, and increased rapidly until death, 72 hours later. The infant was feeble at birth, and toxicity increased with the jaundee. The extremities were limp and atomic, and reflexes were depressed, no signs of increased cerebral tension were present, and there were no convulsions. Spleen and liver were palpable and the splenic enlargement became quite marked. The infant refused the breast, and was fed with difficulty from a medicine dropper. Meconium stools were passed, and the urine was a dark yellow brown color. The temperature was normal throughout Twenty e.c. of whole blood were injected intramuscularly into the gluten, with no favorable response on the part of the infant, who became moribund and expired 72 hours after birth.

The blood findings were as follows: Hemoglobin (Sahli) 56 per cent, red blood cells, 2,510,000, of which there were between 90,000 to 115,000 nucleated red blood cells per cubic millimeter. There was marked variation in the size, and slight change in the shape of the erythrocytes, and diffuse basophilia, and the immature cells varied from very early procrythroblasts to normoblasts. Occasional punctate basophilia was noted (Fig. 3)

The white blood cells numbered 25,600, and the differential count showed 58 per cent polymorphonuclear neutrophiles 1 per cent cosmophiles, 36 per cent lymphocytes, and 5 per cent large mononuclear cells Platelet count was, 75,000 per cu. mm Coagulation time was prolonged to 10 minutes, 30 seconds, and

bleeding time extended over 234 hours. Fragility test—hemolysis starts at 0.42 per cent. Urine gave a 2 plus bile test, otherwise normal

Postmortem Examination—(Dr Paul Cannon, at Chicago Lving In Hospital.) Gross Anatomy—Well developed full term male infant weighing 4016 gm Marked generalized icterus gravis over the skin of entire body are bluish mottlings. There is marked edema of the subcutaneous tissues. The scrotum is engaged with fluid. There are no external marks of trauma, except needle puncture marks in the buttocks. Umbilical cord appears normal Subcutaneous tissues contain more than normal amount of fat.

Abdominal Cavity -It contains about 10 ec. unclotted blood together with blood clots in the dependent portions.

Pleural Cardy -- Free from fluid but parietal pleura contains diffuse areas of ecchymosis. The muscles are extremely pale

Larynx and Trachea.-The truchen is stalued greenish

Esophagus -The esophagus is normal.

Thyroid and Thymus.-The thymus shows diffuse exchymotic hemorrhages.

Heart, Aorta and Vessels.—Foramen ovulo is anatomically patent. The right atrioventricular cusps are normal. Heart weighs 30 grams. All orlices and cusps appear normal. The myocardium is extremely pale and is stained yellow

Lungs.—The visceral pleura contains numerous ecohymotic hemorrhages together with occasional larger areas of hemorrhage. The epicardium also contains diffuse seechymoses. The lungs are not collapsed but air containing. They show no areas of consolidation or atclectasis. Cut surfaces are stained yellowish green and con tain ecchymotic hemorrhages from 1 to 5 cm. in diameter. Lungs float in water The bronchial nuccosa contain fine petechial hemorrhages. Left lung weighs 29 grams, the right 42 grams.

Liver—It is enlarged and on the superior surface of lower lobe is a circum scribed area of white fibrous thickening extending about 1 mm. into liver substance. Liver tissue is greenish brown and is practically free from blood and weighs 240 grams. The gall bladder contains about 2 e.e. of bile which is extremely greenish and viscal. The bile duets are patent and no obstruction to biliary or hepatic duets could be found.

Spices —The spicen is greatly enlarged and weighs 42 grams, is purplish and firm. Out surface is cynactic and firm, and shows no gross abnormalities. Out surface also is rather day

Pancreas -- Appears prossly normal.

Castrointestinal Tract - Stomach, duodenum appear normal. The renal venus anterior to north The retroperitoneal tissue contains localized areas of hemorrhage

Advends — The advends are greenish, but appear otherwise normal. They weigh 7.5 grams. The left ureter is dilated to diameter of 6 mm. The right is normal in size

Kidneys—The left kidney is extremely green particularly the cortical tissue being discolored Otherwise appears normal Right kidney resembles the left and together weigh 45 grams. The right tunical vaginals tests contains about 5 c.c. of clotted blood The left tunical vaginalis contains 2 cc. of a greenish colored fluid

Brais and Meninges.—Skull and eranial tissues stain greenish and contain numer ous petechial hemorrhages, particularly prominent in the temporal muscles. On opening the skull there is marked edema of leptomeninges which are stained green ish. Both hemispheres are pule. The leptomeningeal vessels are much paler than normal. There is no subdural hemorrhage. Falx cerebrum is greenish and contains no hemorrhages. The tentorium cerebelli are intact. There is increased amount of

greenish stained fluid just beneath tentorium. The brain is extremely edematous. The lateral ventricles contain normal quantity of greenish fluid. The brain tissue proper is extremely soft and greenish yellow.

Histologic Examination Liver—Shows a great many areas of large cells with deeply strining nuclei, which are embryonic blood forming cells, forming hematopoietic foci (Fig 1). These hematopoietic areas are thickly scattered throughout the liver tissue in the triads and various parts of the liver lobules. There is considerable destruction of liver cells, most marked in the periphery of the liver lobules. The liver cells contain considerable light brown staining pigment (bile pigment), and considerable deposits of greenish pigment (iron) are scattered throughout in the reticuloendothelial cells. Many of the bile capillaries contain bile thrombi, both in the areas where there is liver cell damage, and also in those areas where the liver cells are uninjured.

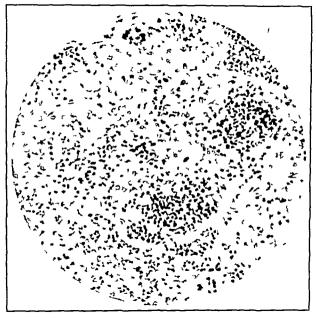


Fig 1—Microscopic section of liver from Case I of icterus gravis neonatorum. Clusters of cells with deep staining nuclei are embryonic hematopoictic foci Deep staining liver cells contain bile pigment. ( $\times 250$ )

The diffuse hemitopoissis, the liver cells filled with bile pigment, the iron deposits, and the bile thrombi are the essential features in the histologic picture of the liver

Spleen—Enormously engorged with blood. Many of the red cells are in physocytes. The red cells appear abnormally granular. There are many cosmo philes scattered diffusely. Young blood cells of all types are evidence of increase of blood forming tissue. Malpighian bodies are small but show no definite changes Germinal centers not conspicuous. Many of the macrophages contain pigment. There are a few cells resembling marroy cells.

Bonc Marrow -Shows normal areas of hematopoiesis of the red and white elements

Jung -Alveeli contain much protein precipitate but there is no evidence of influmnation. Most of the alveeli are expanded

Thymus —Contains large numbers of cosmophiles especially in the stroma There is some interstitud hemorrhage and edema No other recognizable changes.

Andrey — Tubular epithelium swollen and granular with much protein precipitate. There are many casts in the straight tubules granular and heavily pigmented. Mostly reddish brown. As inflammatory changes.

Parereas.—Occasional cosmophile scattered throughout the strome and in the islets. No other recognizable changes.

Adresal—The cells in the central part of the cortex are much vacuolated and seem to be somewhat disintegrated. There are a few small areas showing extravasation of blood. No inflammatory changes.

Cerebellum -No changes, except that some small vessels contain hyaline thrombi-

CASE II -Clinical Illatory - (From the I remature Ward Sarah Morris Children . Hospital. Service of Dr. J. Gerstlev). A white female premature infant weighing 2130 gin of eight months gestution was born on April 20 1933 the seventh child I regumner was uneventful labor was precipitate and rapid. Both the mother s and futher s Wassermann and Kalin reactions were negative. There were six previous pregnancies in this family. The first child born twenty-one years ago was a full term infant became jaundiced on the second day and died on the third day of life the second child was born nineteen years ago on eight months premature stillbirth not jaundled and no edima noted the third child was born seventeen years ago no mundice noted died of pneumonia on the twelfth day of life the fourth child was born fifteen years ago a full term infant jaundiced on the second day and died on the fourth day of life the fifth child was born twelve years ago a full term normal male infant living and well the sixth child was born eleven years ago a full term male infant jaundice was noted almost immediately after birth Red Hood cell count 1 100 000 white blood cell count 9 800 P,M N /1 per cent lymphocytes 27 per cent cosmophiles 1 per cent and myclocytes 1 per cent. The infant was given several transfusions of mother's whole blood intrasinously and recovered. The child is now living and well and normal in all respects. There was no lustory of hydrops universalis in any of the e children in this family

The premature infant here reported was transferred to the premature station where a progressively deepening jaunalie developed. The liver was palpable two finger I readths below the costal markin and the edge of the spicen was firm. The infant was fed with difficulty meconium stools were passed and the urine stained the dispers darkly but none could be obtained for examination. Tenice of whole blood were injected intransactions on April 20 and tenice were given on April 22. The infant bled profusely from the nose and expired 48 hours after birth

The blood fadings were as follows. At 8 hours of age homoglobin (New comber) was 4t per cent red blood cells 2 60 000 of which there were 113 000 nucleated red blood cells per cubic millimeter. There was marked polkilocytosis and slight aniscocytosis, there was diffuse biasophilla and many reticulated red blood cells were demonstrated with vital staining. Then were numerous very carly nucleated red blood cells. The white blood cells numbered 22,500 and the differential count showed 54 per cent polymorphonucleur neutrophiles. I per cent cosmophiles aper cent involved the per cent myelocytes and per cent myelocytes. 2 per cent myeloblasts 31 per cent lymphocytes and per cent large mononucleur cells. Congulation time was over 10 minutes and bleeding time extended over one hour. Fragility test—hemolysis started at 0.50 per cent and was complete at 0.34 per cent.

Icterus index was 123 units and both the indirect and direct Van den Bergh renetions were immediately politice. At death 48 hours after birth the red blood count had dropped to 790 000 and the hemoglobin to 22 per cent (Newcomber)

Blood Iron—Blood iron determined by the Fowenther method was 405 mg per 100 ec at 8 hours of age and 159 mg per 100 ec at 48 hours Calculated hemoglobin from blood iron was greatly higher than hemoglobin determined by the Newcomber method

BLOOD IRON AND CALCULATED AND DETERMINED HEMOGLOBIN

	BLOOD IRON MG/100 C C	GM /100 C C	HGB (CAI CULATED) GM /100 C C	HGB RATIO
8 hours	40 5	8	13 5	1 16
48 hours	15 9	35	5 3	1 38

(Calculated hemoglobin in grams per 100 cc is obtained by multiplying blood iron by factor 335)

#### POSTMORTEM EXAMINATION

(Dr Marion Corrigan, at Michael Reese Hospital)

Gross Anatomy—The body is that of a fairly well developed, premature (seven months' gestation) female infant weighing 2000 grams and measuring 48 cm. Liver and rigor mortis are absent. The skin and sclera are deeply interior. There are several punctate hemorrhagic spots on the skin of the forchead.

On section, the skin is clastic, the subcutaneous fat tissue negligible. The pleural, pericardial, and peritoneal cavities show no gross changes

The heart is of normal size. The valvular apparatus is intact. The myocardium is firm brownish red. The foramen ovale and ductus arteriosus are patent. The intima of the entire aorta is colored deep yellow.

The lungs are semi firm. The pleural surfaces are smooth. The surfaces of the lungs are mottled and dark red. Only small portions of the lung margins are pink gray. The sectioned surfaces are dark red, smooth but for occasional small raised granular areas. The tracker and bronch show no changes

The liver is firm, brownish red, and the surfaces smooth On section, the surfaces are brownish red, the markings poorly defined. The gallbladder and bile ducts show no changes. The liver weighs 110 gm

The spleen is markedly enlarged and weighs 50 grams. It is purple red, and on section the trabeculae are easily discernible, the follicles obscure

The lidneys are purple gray, firm, and lobulated On section, the medulla is well defined from the cortex. In the medulla are glistening plaques of vellow tissue The pelves, ureters, and bladder show no changes

The uterus, tubes, and ovaries show no changes

The pancreas, adrenals, and thymus show no changes

In the mucosa of the eleum are a few hemorrhagic areas, otherwise the gastro intestinal tract shows no changes

On opening the calvarium, the meninges are seen to be somewhat hyperemic In the basal nuclei are shining yellow streaks and plaques, Kern icterus There is no evidence of hemorrhage

The marrow of the long bones appears deeply red

#### HISTOLOGIC EXAMINATION

Heart—Sections of the myocardium stained with hematoxylin eosin show no histopathological changes other than the presence in the blood vessels of many immature cells

Lungs—There is some extravasation of red blood cells into the subpleural spaces. Most of the alveoli are filled with red blood cells and dark brown granules. These

granules are largely free in the alveolar spaces a few being mononuclear cells. The bronchi contain many red blood cells and masses of pink stanning material (fibrin) in the messes of which are mononuclear cells. At the margins of the hemorrhagic areas the alveoli are dilated and confuent.

Liver—The sections stained with hematoxylln-cosin show the evtoplana of the parenchymal cells vacuolated and containing numerous dark brown pigment granules. The sinusoids are dilated, the Küpffer cells filled with brown granules. In the bile explilaries are many bile thrombi. Scattered through the sections are accumulations of cells located in the sinusoids. In sections stained by the Gleman method these cells show the characteristics of myclocytes nucleated red blood cells undifferentiated mononuclear cells, and occasional large polynuclear cells (megakarvocytes)

Spices.—In the sections of spicen the differentiation between follicles and pulp is obscured, the Irmphoid tissue diffuse. Throughout the sections are seen many immature cells and a large amount of brown pigment some of it within mononuclear cells, some extracellular.

Addreys —In the tubules close to the glomeruli the lining cells are swellen al most obliterating the lumina. Occasionally the ertoplasm of these cells contains dark brown granules Stained by Mallory's ferrocyanide method, these granules appear Prussian blue (fron)

Suprarenals -There is some extravasation of blood into the medulla.

Panercas and Thymus - No histopathologic changes.

Boncs.—(Femur) The epiphyseal lines are fairly straight. The medullary spaces are filled with mature and immature cells and occasional esteoid giant cells. Many cells are seen very close to the periostenm.

Brain.—The sections through the basal nuclei reveal some increase in vascularity. There are dark brown pigment granules within the ganglion cells

#### REVIEW OF CUINICAL SIGNS AND SYMPTOMS

The most striking clinical manifestation of interus gravis neonato rum is jaindice. It may be faintly present at birth but rapidly in creases in severity and intensity during the first hours after birth. It is unusual for the interus to develop later than the first twenty four hours after birth which is a differentiating feature from physic logic interus neonatorum which generally appears after the third day of life.

The rapidly developing interus stains the skin, sclerae and mucous membranes to a deep vellow brown color which reaches great intensity within twenty four to forty eight hours after birth. This extremely rapidly developing and pronounced jaundice is the most striking sign of the disease.

Many of the reported cases of interus gravis neonatorum have been well-developed, full term infants as the case of the infant here described though a considerable number have been prematurely born Symptoms of the disease are often present at birth the cry may be feeble the infants are often drowsy and toxic difficult to arouse refuse or are unable to take the breast or bottle. In contrast to those with somnolence, flacedity and hypotometry some occasionally develop clonic contractures opisthotomos and generalized convulsions as signs of cerebral irritation. These latter manifestations are par

ticularly associated with those infants who develop the nuclear of "Kern leterus" 16 1 18 No one who has ever seen such a newborn infant, afflicted with this intense jaundice, will deny that the infant is desperately ill

Occasionally a slight edema may be noted in these jaundiced infants which is of quite a mild degree, and involves the extremities, chiefly the hands and feet Petechiae and more extensive eachymoses have also been noted on the skin as well as hemorrhage from the mucous membranes of the mouth and nose Bleeding has also been reported from the umbilical stump and intestinal tract, and is probably associated with the prolonged bleeding time frequently noted

Cases of icterus giavis neonatorum have been reported, as of either familial or sporadic type, in fact its occurrence in successive pregnancies has led to the inclusion of the "familial" or the "habitual" type of icterus giavis neonatorum as a descriptive title of the disease Nevertheless, sporadic cases are of recognized occurrence

The disease is known to occur in many races and cases have been reported from infants of English Dutch German, Scandinavian, Russian, and Italian parentage. The first cases reported in the American literature were in 1916. Recently an authentic case of Chimese parentage has been reported. DeLangeo reports a family in Groningen in which a mother lost two children with reterus gravis neo natorum in preceding pregnancies, and was finally delivered of twins. The first a boy, developed reterus gravis neonatorum and the second, a girl, was born with hydrops congenitus universalis.

Hilgenberg<sup>22</sup> reports a mother who had several normal children by her first marriage, and gave birth to six infants who died of icterus gravis neonatorum by her second marriage. On the other hand, E. V. Gierke23 reports the case of a father who had a normal daughter by his first marriage, and by his second wife two newborn infants who succumbed shortly after bith and were found at autopsy to have suffered with icterus gravis neonatorum. There is good evidence then to point to the familial nature of the disease, though sporadic occurrences have also been noted The two families quoted in which second mairiages occurred might point to a hereditary factor. In Hilgenbeig's report the mother had normal children by her first mairiage, and the second husband would be implicated. On the contrary, in V Gierke's report the father had a normal daughter by his first wife, so that the wife of the second marriage would be suspected of the hereditary transmission Though the familial tendency can be definitely stated, there are too few reports to assume a hereditary transmission

Besides the signs and symptoms already mentioned, enlargement of the liver and spleen is usually noted, the latter being enlarged considerably, and of a firm consistency Hematologic findings are of great interest. The anemia is of a severe degree and the pallor is quickly masked by the deep jaundic. It is of a hyperchronic type the color index being 1 or above. There is a rather marked poskilocytosis with only slight anisocytosis. The white blood count is moderately increased with little change in the differential count, and occasional importure white cells are found.

The most important and characteristic change in the blood picture is the enormous number of immature and nucleated red blood cells found in the circulating blood, from 50 000 to over 100 000 per cu min. They vary from the very early erythroblasts to normoblasts and bisophilic red cells and the nuclei of these immature erythrocytes show many mitotic figures. A few of these early crythrocytes are probably procrythioblasts. A possible relationship between the presence of these many immature crythrocytes in the blood with the extramedulary crythropieses will be discussed later. A greatly in creased number of reficulocytes may be demonstrated in smears stained with vital stains.

The platelets are diminished in number averaging 80,000. Combined with this relative thrombopenia we note a slightly increased clotting time and a greatly increased bleeding time, which probably accounts for the tendency to skin ecclymoses hemorrhage from the nucous membranes and the petechnae found on the internal serous surfaces and in the viscera. The first blood iron determinations to be reported in a case of icterus gravis inconatorum, are those from Case in here presented. The blood iron values obtained were considerably higher than would be expected for the determined grams of hemoglobin per 100 c e (Newcomber)

The resistance of the red blood cells to various saline concentrations is little changed. The interns index of the blood scrum is greatly increased and a biphasic Van den Bergh reaction is usually present. The Wassermann and kahn blood reactions in these cases are both negative. We may summarize the characteristic blood findings as severe hyperchronic anemia of homolytic origin marked erviting blastic blood picture as evidenced by the immature red blood cells, increased number of reticulocytes, thrombopenia and greatly in creased bleeding time, and an increased amount of bile pigment and iron in the circulating blood.

The name has in the majority of cases shown a positive test for bile pigment indicating the obstructive as well as the hemolytic origin of the jaundice

The placenta has been reported as cularged in a number of the reports 2 4 10 11 with a vellowish vernix caseosa covering the infant at birth

A fatal outcome has ensued in the majority of reported cases though the eventual termination may depend upon the severity and

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Besides the signs and symptoms already mentioned, enlargement of the liver and spleen is usually noted, the latter being enlarged considerably, and of a firm consistency The liver cells, themselves, have been found to be deeply stained with bile pigment. There are areas of liver cell damage, marked by cell necrosis and some fatty degeneration of the liver cells. The Kupffer cells contain considerable amounts of iron pigment.

Bile thrombs crowd the bile capillaries, and have been reported in numerous cases (see Fig 2). Iron deposition in the reticuloendothelial cells is pronounced and is associated with the phagocytosis and lysis of the crythrocytes in these cells.

Spleen and kidneys show marked accumulations of iron pigment, as well as some extramedullary hematopoietic areas, as do the pancreas, thymus, adrenals and some other organs 2, 2, 4, 2, 11

The bone marrow may show normal to mereased 116 degrees of white and red blood cell hematopoiesis and some diminution in the mega karyocytes. 4 5 11

#### THEORETIC DISCUSSION OF LATHOLOGIC PINDINGS

It would be interesting to speculate on the relationship of the various pathologic findings and I offer the following theoretic possibilities

1 Ieterus —As has been previously noted, Mann's and his coworkers have shown that hemoglobin is broken down in the reticuloendothelial cells and in the blood stream, to form bilirubin which is then taken out of the blood by the epithelial liver cells and is stored and excreted by them into the bile capillaries and thence into the larger hepatic ducts. The epithelial liver cells, therefore do not form or secrete bilirubin they simply store and exercte this pigment.

Similar in many ways to kidney excretion, the liver cells must excrete the bilirubin brought to them by the blood stream and jaundice will not occur if excretory demands are sufficiently met in the absence of obstruction of the bile passages. It might be possible that jaundice in the absence of obstruction can then be caused by bilirabin being produced faster than normal liver cells are able to excrete it ther it might be caused by disturbed or damaged liver cell excretory ability with a normal rate of formation of bilirubin which cannot be removed satisfactorily. It can be further pointed out that there may be an actual diminution in the number of liver cells through destruction or necrosis without a resulting jaundice if the remaining he patic cells are able to excrete bilirubin normally However while a damaged liver may be capable of ridding the blood of a normal amount of bilirubin such a liver would be unable to excrete an excess produc tion of this pigment and jaundice would result from the retention of thus material

I have previously pointed out that normally with the onset of labor a gradual and continuous destruction of the polycythemic fetal blood occurs, and blood destruction goes on in the newborn at an increased This must result in an increased bilirubin formation during the first few days of life, and is probably one of the chief causes of physiologic acterus neonatorum. A damage to the epithelial cells of the liver in acterus gravis has been described since the early report of Pfannenstiel and has been confirmed by nearly all subsequent reports. The increase in bilirubin formation together with the damaged liver cells, may produce acterus in the absence of obstruction to bile ducts. This may be demonstrated by an indirect Van den Berghreaction presence of increased urobilin and absence of bilirubin and bile salts in the urine. This would not explain the bile pigment in the urine, and the positive direct Van den Berghreaction.

The presence of bile thrombi in the bile capillaries (Fig. 2) will aid in this explanation. The direct Van den Bergh reaction and the presence of bile pigment in the urinc can only be accounted for on the basis of an obstruction to the flow of bile in the bile passages. Bloom<sup>28</sup> has shown that following complete obstruction of the common bile duct experimentally, the increasing amount of bilirubin in the blood gives at first, only the indirect and later the biphasic Van den Bergh reaction. The obstructed bile fills the small bile ducts and diffuses into the lymph spaces and then into the blood stream. An actual rupture of the bile capillaries need not take place. The plugging of these bile capillaries by bile thrombi may be sufficient to cause a reflux of bilirubin into the lymph spaces and blood stream.

As an explanation for the jaundice, we may, therefore, conclude that an increased bilirubin production, and an impaired excretion result in a retention reterus the bile thrombi explain the obstructure or regurgitation reterus, and all signs and tests indicate a combination of these two mechanisms in the production of jaundice in icterus gravis neonatorum

I have accounted, in part, for the increase in bilirubin excretion, as a physiologic phenomenon, occurring normally at birth. What causes the liver cell damage and what the bile thrombi?

It is apparent from a microscopic examination of the liver that we are dealing with an organ abnormal for a full-term or premature infant. The tremendous number of hematopoietic foci simulate the embryonic organ of a fetus of from three to five months' gestation <sup>5</sup> <sup>20</sup> I can only believe, from a study of the cases in the literature and those here reported, that we are dealing with a fetal type of liver, which for unknown reasons, has failed to mature properly. There is no evidence to suggest that the liver has developed normally, and that the hematopoietic foci are of a compensatory nature. The bone may row shows no changes indicating incapacity. Further, any such compensatory process developing shortly before and after birth would hardly be conceivable in so short a time.

Another explanation offered suggests that the overcrowding of the liver with hematopoietic foci could cause pressure atrophy and dain age to the liver cells enough to cause obstruction as well as hemolytic jaundice. If this were possible, would not every embryonic liver be overcrowded would not obstructive jaundice occur in every leukemic infiltration in Niemann Pick's disease in every metastatic liver careinomatosis and in diffuse hemangic endotheliomata.

An arrested fetal development of the three may be due to a defective anlage and possibly the familial occurrence of this condition may be sought for in germ plasm defect. Toxic influence early in pregnancy as an congenital syphilis might also retard liver growth and cause the arrested fetal development.

It may be supposed that in this condition the embryonic liver takes care of bilirubin exerction until near the end of pregnancy be it of premature or full term duration. The fetal hematonoietic foci in the liver augment the blood cell formation from the bone marrow and immature red blood cells are thrown into the circulation t bilirubin formation added to decreased ability of epithelial liver cell exerction must lead to an intrauterine bile retention This we may Accumulation of excess bilirubin in the bile capil laries perhaps mixed with a foreign protein substance. 28 leads to coagulation of bile pigment in the bile capillaries and thus to bile Occlusion of the bile capillaries by bile thrombi leads to a diffusion of bilirubin into the lymph spaces and into the blood stream and thus we have bile requirification. Stage II. Though the fetal kid. neys secrete but little urine, there is proof that the amniotic fluid contains some fetal urine in The bile regurgitated into the blood stream is eliminated by the fetal kidney into the amniotic fluid. This explains the beer brown emmotic fluid and the golden yellow vernix The increased number of fetal erythrocytes reduces the oxygen-carrying power of the blood and by increasing anoxemia may cause the enlargement of the placents noted in this disease and in concenital hydrops neonatorum 4 10 11

Should the process only proceed as far as Stage I due to the ability of the liver epithelial cells to exercte sufficiently to keep up with bilirubin formation an infant will be born with only a variable degree of hemolytic or retention interial which may not be present at birth and which will probably be a mild form of interial gravis neonatorium with a favorable chance for recovery. This also answers klemperer satequery as to the differences in liver pathology which may occur in this disease. Returning to the question what causes the liver cell

The most common pathologic change in the liver of congenital syphilis, is its nevel returnistion of development. The liver in newborn concentral syphilis is still softly engaged in blood formation. MacCallum— states—There is nothing clearly specific about such an natonic picture—the same thing may be found in a normal fectu of a rather early r stage of teclorment, but the abundant distribution of spiro chetae through the tissu 1 termines its syphilitic nature

damage? There may be impairment of the excretory power of the liver cells in anemia, and also in anoxemia <sup>26</sup> The increased number of circulating immature erythrocytes may augment fetal anoxemia, due to the less efficient oxygen-carrying power of young forms of red blood cells

The resulting anoxemic increase could produce liver cell damage, as MacCallum<sup>326</sup> and others have pointed out that damage to liver cells, especially in the area about the central efferent vein of the lobule, may be due to an insufficient supply of oxygen

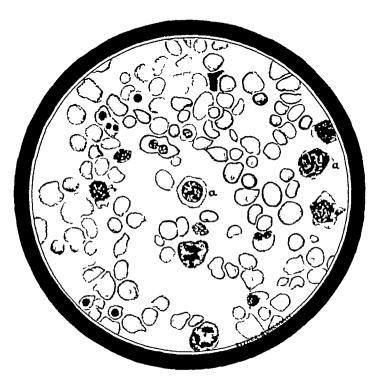


Fig 3—Blood smear from Case I of icterus gravis neonatorum at twelve hours of age. 90 000 nucleated red blood cells per cubic millimeter megalobiasts and normoblasts several of the latter undergoing cellular division. (a) are early erythroblasts May Grunewald Glemsa stain

In some of the cases reported, the liver cell necrosis has been central, and anemia and anoxemia may account for this cell damage (Klemperer<sup>31</sup>—case 2) Bile stasis could probably also contribute to liver cell damage and necrosis Beginning with the arrested fetal development of the liver (possibly due to a defective anlage or toxic influence in early fetal development), I have thus far been able to offer a theoretical explanation for the jaundice the immature erythrocytes in the circulation, the degrees of jaundice with which the infant may be born, the variable antenatal severity of the disease, the familial incidence, the coloring of the amniotic fluid and vernix

caseosa the enlargement of the placenta, the bile thrombi, the liver cell damage, and the occurrence of a retention, as well as a regurgita tion type of laundice

We may explain the occurrence of sporadic cases on the assumption of toxic influence in early pregnancy rather than defective anlage

2 The Iron Psymentation—This finding in the various organs may be due to the increased hemolysis of the red blood cells both in the circulation and in the reticuloendothelial cells, and may also be due to an increased phagocytic action on the part of this system. The increased destruction of red blood cells in the polycythemic fetal blood with the excess liberation, and destruction of hemoglobia, accounts for the increased iron in the circulation (Case II) and in the tissues. The breakdown of the excess hemoglobia liberates iron and this is picked up from the circulation by cells in the liver, spleen, kidney, tubules pancreas thyroid and other organs. The tissues of the body are simply o ersupplied with iron, because of the excessive hemolysis of red blood cells and the resulting breakdown of hemoglobia through out the circulation.

This whole process is in its essential points merely an accentuation of the hemoglobin destruction and iron storage, which normally occurs in the newborn period. Gladstone<sup>22</sup> has recently reviewed this subject, and pointed out that Bunge's storehouse theory no longer holds, and that the newborn infant is not born with a fetal iron depot. It creates its own iron deposits after birth through the excess hemoglobin liberation and destruction when the change from the newborn polycythemia to the normal postnatal values for hemoglobin and red blood cells are taking place. Oxygen tension regulates this normal decline from the antenatal anoxemic fetal polycythemia to the post natal values commensurate with the environmental oxygen tension of air.

3 Erythrocyte Resistance—The relative fragility or resistance of immature erythrocytes also deserves discussion. DeLange' has suggested that the youthful red cells have a greater resistance to hemoly sis than mature erythrocytes. It has been mentioned that in intering gravis neonatorium the fragility tests of red blood cells against various concentrations of saline solution varied little from normal. However on closer analysis more facts are known than this, so that simply testing the red blood cells to saline dilutions and drawing conclusions from such tests is not enough. DeLange's suggestion of an increased resistance of youthful red blood cells is also held by Anselmino and Hoffmann. Who propose the theory that the increased resistance of the youthful forms is offset by the decreased resistance of the older red blood cells. However recent investigations tend to prove that exactly the opposite phenomenon is true namely that the youthful red cells have a diminished osmotic resistance as compared to mature

erythrocytes<sup>3</sup> This decreased resistance might aid in explaining the rapid disappearance of the youthful forms<sup>36</sup> Also any increased resistance would then be due to the older red blood cells. The whole subject of the normal osmotic resistance of the various aged erythro cytes as well as the changes in resistance which may occur in jaundice and other pathologic conditions needs much experimental proof, before conclusions can be adopted with certainty

4 Anemia —Discussion of the cause for the anemia in icterus gravis neonatorum may be brief, as the underlying factors have been already

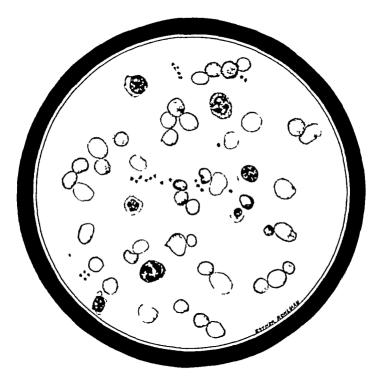


Fig 4—Blood smear from a case of anemia of the newborn at nine days of age Hemoglobin 24 per cent red blood cells 1 270 000 nucleated red blood cells 7800 per cubic millimeter May Grunewald Giemsa stain

traced in detail in the explanation of the occurrence of other signs and symptoms. It is assumed in this condition, that a normal polycythemia exists in the fetus, associated with circulating immature red cells.

The anemia is of a hyperchiomic type, and the normal appearing hyperplastic bone marrow precludes an aplastic type of anemia. The normal fetal anoxemia is probably increased by the poorer oxygencarrying capacity of the immature crythrocytes. The red blood cells in the reduced oxygen tension of high altitudes show, besides the polycythemia, some poikilocytosis, and hyperchiomic characteristics. In

this type of polycythemia the color index is high, as it is also in the normal newborn. Even at heights over 7500 meters, nucleated red blood cells have not been found after careful and particular search <sup>37</sup>. The ervthrocytes at high altitudes show outspoken regenerative, but no degenerative changes. The animin of retering gravis meonatorium is also of a hyperchronicity pe with no degenerative signs. The enormous increase in nucleated red cells is therefore net associated with lack of oxygen, polycythemia bone marrow failure or developmental failure. The fetal extramedullary foer produce fetal types of nucleated red cells which may flood the circulation. When hemolysis begins with the

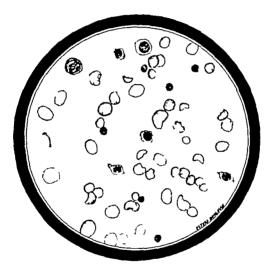


Fig. 5—Blood amour from a case of congenital 3 phills in a number infant 3 Sects of age. Henographic 30 per cent red blood cell 1 30 000 much ated ted blood cell 40,000 per cubic millimeter. Many normoblasts and extra ki nuclei. Wirkin than,

onset of labor as in normal newborns there is a rapid destruction of mature and youthful red cells. If we assume that the immature forms are more fragile they must be destroyed at a more rapid rate in the increased oxygen tension after the onset of labor. The process is much too rapid for compensatory regeneration to be of immediate influence though in infants who survive compensatory regeneration will aid after some weeks of life. The increasing jaundice probably adds to red cell fragility and increases the rate of hemolysis of the red cells. Extremely rapid red cell destruction for the reasons stated

accounts for the anemia. The circulating nucleated red blood cells are present in great numbers, for the same reason that they are similarly increased in other diseases where an embryonal persistence of hematopoiesis occurs, associated with enormous numbers of extramedulary blood islands (Fig 5). The cause of the arrested hematopoietic development is different in icterus gravis neonatorum, than it is in congenital syphilis, yet the source of the great numbers of nucleated red cells is probably the same in both cases. There is no necessity then, for assuming a primary metabolic disturbance of the entire hematopoietic system, or a compensatory origin of the extramedullary blood islands 38. Hematopoietic foci are specific for, and outstandingly characteristic of, fetal liver. We have therefore, gone one step farther in the explanation of this condition, and if the facts be correct, the theoretic considerations must commence with the cause for the persistence of the embryonal type of blood formation.

## ASSOCIATION OF ICTERUS GRAVIS NEONATORUM WITH OTHER ENTITIES

A Nuclear Icterus — The occurrence of nuclear or kern icterus associated with icterus gravis neonatorum opposably depends upon the degree of jaundice. The condition never occurs in an adult, and is not exclusively linked with icterus gravis, as it has been noted in the brains of children dying after physiologic icterus neonatorum opposable to the central nervous system, which occur in some of the infants surviving icterus gravis neonatorum. In Case II, here reported, a Kern icterus was found

B Hydrops Congenitus Universalis —The similarity of hydrops congenitus universalis to icterus gravis has been pointed out in a number of reports <sup>2</sup> <sup>11</sup> In the former condition a dropsical infant is still-born, dies during birth, or may be delivered dead by cesarean section. The edema is universal and marked, there is pallor, and icterus may be slight, as noted in the edematous tissues. The blood from heart puncture shows greatly increased numbers of circulating immature erythrocytes. Pathologically the examination of the organs is similar to the changes found in icterus gravis. There are many petechial hemorrhages and ecchymoses. Extensive extramedullary hematopoiesis and hemosiderosis have been noted microscopically.

The liver shows the same number of hematopoietic foci as the liver of icterus gravis, and necrosis of liver cells and bile thrombi occur as frequently. It is interesting to note the occurrence of bile thrombi in combined reports of the two conditions. In reporting four cases of icterus (3 own and 1 literature), DeLange and Arntzenius noted bile thrombi in 4 cases out of 4. In reporting 6 cases of hydrops universalis where mention was positively or negatively made as to the occurrence of bile thrombi (1 own case and 5 literature), the same

authors reported their presence in 3 out of the 6 Salmonsens noted bile thrombi in 2 out of 5 of his reported cases of hydrons congenities Ferguson, noted bile stasis and thrombi in the bile capillaries in 2 out of 3 cases of acterns gravis, and none in two cases of hydrons con genitus Diamond Blackfan and Baty12 report the autopsy protocols of 4 cases of acterns neonatorum gravis of which 1 (Case 9) was reported as having many bile capillaries distended with bile. Slight edema has been noted in cases of icterus gravis neonatorum 5 f 8 9 11 In Case I here reported edema of the subcutaneous tissues was noted and the scrotum was encorned with fluid. The edema may be accounted for by such factors as severe anemia anoxemia or by an abnormal albumin globulin ratio, which have been used to explain edema associated with other anemias.11 Since Plaut's reported siblings with acterns grayis and hydrons congenitus, other instances of the two diseases in the same family have been noted 5 11 DeLange has reported twins one with icterus gravis and one with hydrons congenitus Common to both conditions are, the familial history, finding of each disease in a sib ling the occurrence of edema in icterus gravis and of mundice in hydrops congenitus, the similar pathology to the minute microscopic details, as hematopoietic foci hemosiderons and bile stasis and thrombi in the bile capillaries and the focal liver cell necrosis and finally, the circulating immature red blood cells. The two conditions must be assumed to be of identical etiology, associated with the persistence of an embryonal liver and blood formation. The more marked edema in hydrops congenitus universalis is probably responsible for the intra uterine death in the majority of these cases

C Anemia of the Newborn—In 1931 Stransky <sup>13</sup> in reviewing the then published cases of this condition, noted the similarity in the pathologic findings reported by Frank<sup>19</sup> and Schleussing <sup>40</sup> to those of icterus gravis and hydrops congenitus. He concluded that there were two types of cases one characterized by an embryonal blood picture and the other designated as an aregenerative type. This analogy has since been made by several other authors <sup>41</sup> <sup>11</sup> In going over the literature I reviewed<sup>42</sup> the autopsy reports of Susstrunk<sup>43</sup> and Schleussing <sup>40</sup> The former noted marked hemoaderous and the latter numerous hematopoietic foci in various organs. Since my report other cases of anemia of the newborn have appeared,<sup>11</sup> <sup>44-50</sup> of which the cases of Paschoff<sup>44</sup> and Happ<sup>50</sup> terminated fatally. The postmortem findings in their cases also showed evidence of a fetal type of hematopoiesis

A familial tendency for the occurrence of anemia of the newborn in siblings has been noted by Diamond Blackfan and Baty<sup>11</sup> (Cases 6, 7 and 8), Segar and Stoeffler<sup>45</sup> in 3 siblings Happ<sup>80</sup> and Boner<sup>45</sup> in 2 siblings each

A further relationship has been noted, in which different offspring of the same mother have suffered either icterus gravis or anemia. In Ecklin's 1 case of anemia of the newborn, the child of the preceding pregnancy had died of icterus gravis and Case 5 reported by Diamond, Blackfan and Baty 11 revealed that the first-born infant died of intense jaundice within 24 hours of birth

It has been noted that many of the cases of anemia of the newborn have shown icterus The second infant reported by Segar and Stoeffler showed an edema of the scrotum on the fifth day, while in Case 8 of Diamond, Blackfan and Batv11 edema of the eyelids and extremities was noted on the third day. We have then, in cases reported as anemia of the newborn a familial, as well as a sporadic type, besides the occurrence of icterus gravis or newborn anemia in offspring of the same mother, and finally the occurrence of edema in cases of anemia of the newborn The anemia which is of varying severity is at first of a mild hyperchiomic type with nucleated red blood cells moderately increased (see Fig. 4) Later the anemia tends to become slightly hypochiomic An infant surviving ieterus gravis will giadually lose the hyperchromic type of blood picture, the immature eryth roblasts will disappear from the circulating blood and a slightly hypochromic anemia will precede the return of the blood to normal Van Creveld'2 has been able to demonstrate these changes by measuring the diameters of the red blood cells in three cases of icterus gravis and in one case of newborn anemia

I would consider the occurrence of eighthrophatocytosis in the peripheral blood as an incidental finding <sup>3-11</sup> and as pointed out this phenomenon has occurred in other unrelated diseases <sup>3</sup>

D Association With Sepsis—Since the review by Knapfelmacher<sup>13</sup> in 1910 sepsis of the newborn has been proposed as the etiologic basis for icterus gravis. Since then I A Abt,<sup>16</sup> Yllpo <sup>26</sup> Kleinschmidt and others have offered clinical proof and negative bacteriologic findings as evidence that icterus gravis is not based on sepsis. G Mever<sup>14</sup> has recently reported two cases of newborn infants with deep jaundice who were shown to have died of generalized sepsis at autopsy. Dunham<sup>15</sup> in a recent report on septicemia in the newborn, reported 12 infants in her series with severe jaundice and 3 instances of liver damage at autopsy (chronic hepatitis diffuse fibrosis and central necrosis)

It cannot be denied that sepsis may cause Jaundice and liver changes in the newborn, and that the clinical and pathologic findings may have some similarity with icterus gravis. However, there have been enough cases of icterus gravis reported, where not even the minutest evidence of infection or sepsis could be found to wairant the negation of such an etiology. Newborn sepsis should be considered in the differential

diagnosis of icterus gravis acounterum is made

F. Prophylaxis and Therapy -Smyth 4 has reported a most interest ing attempt at prophylaxis in icterus gravis neonatorum. An Australian mother had previously given birth to nine infants, the first two chil dren were normal and survived there was one stillborn premature birth and 6 infants had developed interus gravis neonatorum and died from 3 to 11 days after birth. A prophylactic attempt to prevent icterus gravis for the infant of the tenth pregnancy consisted of hos pitalization of the mother through the entire course of her pregnancy with extremely careful supervision and regulation of her diet mother was perfectly normal during her term of pregnancy days before labor was due a cesarcan section was performed and a normal female infant was delivered The mother's tubes were ic sected and tied. The infant remained normal for twenty four hours when it became drowsy and progressively interic and died 70 hours after birth

This report is most instructive. It demonstrates the remarkable familial occurrence of the condition and the fact that the most care ful supervision of the mother gives no clue to the disease of the fetus. The cesarean section precludes all possibility of a vaginal infection of the infant and is strong evidence against the septic origin of the disease. Further the resection and tying of the tubes in a woman who has had eight newborn infants die out of 10 pregnancies would seem a wise eugenic procedure.

Bernheim Karrer and Grob<sup>53</sup> have reported the daily feeding of 100 grams of liver to a mother during the last 10 weeks of her pregnancy who had previously given birth to two newborn infants dying of intering gravis. A normal infant was born following the liver feeding prophylaxis but no conclusion can be drawn from such an isolated instance as in Smyth s<sup>54</sup> case the mother was also fed liver during her pregnancy, and the infant born died of intering gravis.

The question of blood transfusion as a therapeutic measure in interim gravis is open to analysis. Infants to whom blood had been given therapeutically have both survived and succumbed. Krainsztykan has reported recovery of a case after intransuscular injection of 10 c c of whole blood. Others have given transfusion and intransuscular blood to these infants with and without success. T 10 11 21 07 (Cases here reported.) Spontaneous recovery has also been reported in cases of anemia of the newborn as well as survival after transfusion.

Splenectomy has been attempted by Cooley in a case of acterus gravis. While the removal of the spleen might slow blood destruction in this condition at could hardly be expected to prove of much and in a severe case. 10

# SUMMARY

In the course of the discussion the similarity in symptoms, signs and pathologic findings, though meager, pointing to the relationship of icterus gravis neonatorum with hydrops congenitus universalis and anemia of the newborn have been brought out A theoretic explanation has been offered to account for the known clinical and pathologic findings in icterus gravis neonatorum. In the absence of definite substantiating facts, a speculative etiology, embryonal persistence of hematopoiesis of eightinocytes has been advanced, which would explain the findings in icterus gravis and the interrelationship of the three conditions on the same causative basis. Beginning with the persistence of an embryonal characteristic in the fetus, the resulting disease may be explained on the degree of the process in each individual case analogy with congenital syphilis, a disease of known etiology, could (a) An extensive early spirochetal action may result here be drawn in a macerated fetus or stillbirth. Early embryonal fetal persistence of hematopoiesis of erythrocytes may result in hydrops congenitus (b) A newborn congenital syphilitic infant may be less severely damaged than the macerated fetus or stillborn, and it may show jaundice, and immature circulating erythrocytes (Fig. 5) embryonal persistence of a somewhat later stage than hydrops congenitus may result in icterus gravis neonatorum (c) A congenital syphilitic infant may show an early severe anemia. A slight degree of embryonal persistence may result in anemia of the newborn

# CONCLUSION

The three clinical entities described as icterus gravis neonatorum, hydrops congenitus universalis and anemia of the newborn show interrelated clinical signs and symptoms, most significant of which are familial occurrence, jaundice, edema, anemia and circulating immature red blood cells (crythroblastosis)

The pathologic findings in these three diseases show a certain similarity, but the facts are too meager to permit drawing definite conclusions, and nothing is known of the essential prenatal pathology of the three diseases

The classification and origin of these three newborn conditions has been vague and uncertain. A theory is offered, embryonal persistence of hematopoiesis of red blood cells in various organs, which would explain the clinical symptoms and pathology common to these three newborn entities

The inferences drawn are purely speculative and must await future pathologic or experimental proof. The origin of the extramedullary hematopoietic foci in the various organs appears to be an embryologic persistence rather than a compensatory regeneration of erythrocytic

While the term erythroblastosis has been used by previous authors, I believe that embryonal hematopoietic persistence would be more accurate and better descriptive of the underlying disturbance

Two cases of icterus gravis neonatorum associated with circulating immature red blood cells in a marked degree are here added to similar cases already reported. The first case was of sporadic occurrence, and revealed no nuclear involvement in the brain, the second was of the familial type and associated with Kern icterus

Blood iron determinations not previously reported for icterus gravis neonatorum were found to be high in the second case here presented

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104 SOUTH MICHIGAN AVENUE

# THE DISAPPEARING TIME OF DYES INJECTED INTRADERMALLY

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S OME of the theories of vital staining have been considered by Krebs and Wittgenstein and von Möllendorff it. For our pur poses we have to keep in mind that the chemical constitution of a dye as such does not seem to have much to do with its distribution that acid and basic does not keen to have much to do with its distribution that size of the particles of a dive in its solution is of importance. Schule mann offered the suggestion that the distribution of various substances in the organism including acid dives might be dependent on their common property of carrying a negative electric charge and their being attracted therefore to anodal regions of the organism

That the electric charge of the particles of die is of the greatest importance to their behavior has been accepted by others as for in stance. Krebs and Wittgenstein, 12, 2 Wertheimer and Fischer 3. The electrical factor has been stressed particularly by Keller. He proposed to discontinue the division of dives into acid and basic dives and to distinguish them according to their migration in the electric field, as cathodal or anodal dives. Most of the acid dives wander to the anode in watery solution, the basic dives to the cathode. But in blood return or in cell plasma the direction of the migration can change so that acid dives become cathodal and basic dives anodal. By means of dives it is possible to determine whether a cell or tissue is preponder antly positively or negatively charged. The importance of such a distinction is readily seen. For instance, according to Keller, a very important factor in the transportation of water in the organism is its migration to the eathode.

buch considerations prompted our experiments to determine whether it was possible to differentiate in this sense an easily visible part of the body for example the superficial layer of the skin. It was thought that intradermally injected does depending on their character might be retained for a shorter or longer period of time (Table I)

The dyes were injected into the skin of the forearm of volunteer subjects, using 0.2 e.c. in a 0.01 100 solution made up in 0.5 100 so

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dium chloride solution Occasionally stronger solutions were used Each dye was tested on at least three persons. Keller tested a large number of dyes on the smelling rods, and their joints, of Daphnia magna, listing those which stained the rods cathodal and those which stained the joints anodal. Of the errors he mentions, we encountered particularly irritation on injection of some of the dyes (Table I)

The group of cathodal dyes contains only acid dies, and the group of anodal dyes contains basic dies with the exception of aurantia (Table I)

The disappearance is often gradual and cannot be determined with great accuracy. The limits of time can be regarded only as approximate, nevertheless, they were sufficiently distinct for our purpose. With Congo ied, for instance, this difficulty depended to a certain extent on the color of the skin of the subject. Proper color filters could be employed with advantage. With brilliant kiesvi blue some color remained for weeks in the needle stab and in a few experiments with isamine blue, for days

The first consideration must be given the degree of dispersion of the dyes, since a coarsely divided dye is more likely to remain at the place of injection. The relative size of the particles has been determined by various methods, such as ultrafiltration, elevation in strips of filter paper, penetration into gelatin, and their rate of diffusion. The degree of dispersion depends also on various factors such as temperature, concentration, reaction, and presence of salts or of colloids.

TABLE I

TIME OF RETENTION OF VARIOUS DYES IN THE SUPERFICIAL LAYER OF THE SKIN

CATHODAL DYES	TIME OF RETENTION	ANODAL DYES	TIME OF RETENTION
Fluorescein Eosin Erythrosin Rose bengal Rubin S Latmus Azolitmin Congo red Trypan red Fuchsin acid Alkali green Water blue Alkali blue	2 to 4 hr 12 hr 48 hr 36 to 60 hr Less than 24 hr Less than 24 hr Less than 24 hr 48 to 96 hr 5 days 2 months More than 1 yr	Malachite green Neutral red Aurantia Aniline green Methylene blue* Neutral acrifiavine Fuchsin basic Dahlia Safranine Brilliant kresyl blue	1 to 2 hr 12 hr Less than 24 hr More than 6 hr 36 to 72 hr 3 to 5 days 5 days 6 days 2 weeks Weeks

\*The methylene blue kept its blue color for this length of time whether any leukobase was formed cannot be said

At present it seems haidly possible to determine the size of the particles very accurately under various conditions, and so it is easily understood that authors differ in the arrangement of the dyes in the order of the size of the particles

Fluorescein is generally said to be finely divided whereas alkaliblue is one of the coarsely divided dyes. Fluorescein disappeared rather rapidly, whereas alkaliblue remained for a very long time But Congo red, rather coarsely divided, disappeared sooner than the more finely divided fuchsin, whereas neutral acriflavine and basic fuchsin disappeared more slowly than the more coarsely divided neutral red. Such observations indicate that the degree of dispersion is not likely to be always the determining factor of the disappearing time.

Some dyes, like rubin S, gave a weak color in the dilution used Bismarck brown and neutral violet gave color that was too weak for reading. In some instances higher concentrations were used. fluorescein, in a concentration of 1 1000 disappeared in seven hours, and aurantia, in a dilution of 1 5000, disappeared in less than twenty four hours Neutral violet, in a concentration of 1 1000 caused irri tation as did a number of other dyes Occasionally, Congo red proved a little irritating in a dilution of 1 10,000. With this dye rather numerous tests were made. Injections of alkali green were followed by some edema Litmus and azolithmin were irritating, although a purified litmus was used. In stronger concentrations, both were very irritating, producing local edema and reddening Elman, Drury and McMaster prepared erythrolem and erythrolitmin from litmus. We used erythrolem in a dilution of 1 2000, but it could hardly be seen and it produced no irritation Erythrolitmin in dilution of 1 10,000 disappeared in thirty to sixty hours. In this dilution it was not irritating Stronger solutions, 1 5000 and 1 1000 were painful and irritating The disappearing time was prolonged, indeed, the injection of 1 1000 could still be seen after months

Litmus azolithmin and erythrolitmin turned blue on injection and remained so. But this can hardly indicate the actual reaction of the superficial skin, since Elman Drury and McMaster showed that erythrolitmin has a great salt and protein error

Safranine, not irritating on injection, produced in all instances slight superficial necrosis with scaling. Neutral acriflavine behaved similarly. In concentrations of 1 1000 it produced infiltration.

Fühner remarked that many dyes are irritating and can produce inflammation. Of our dyes aniline green produced by far the most intense reactions, being also very painful on injection. In a few experiments with rabbits the effects of its instillation into the conjunctival sac, and of its intracutaneous injection, was compared with malachite green and iodgreen, also basic dyes. In a dilution of I 10 000 these latter dyes did not produce inflammatory reactions, while aniline green did. In stronger concentrations, aniline green produced hemorrhagic inflammation in joints and the pleural cavity

It may be mentioned that iodgreen, injected into one subject, disappeared within twelve hours

Comparing the disappearing time of fluorescein, rose bengal, eosin, erythrosin, and fuchsin S, all cathodal dyes, with that of neutral red, basic fuchsin, methylene blue and perhaps acrifiavine and safranine, all anodal dyes, it appeared hardly possible to distinguish the superficial layers of the skin in the sense which Keller meant. The more coarsely divided dyes were left out of consideration. Neither acid nor basic fuchsin was discolored. The colorless carbinol of fuchsin was not restored to color. According to Karczag, this would indicate indifference with regard to electric charge.

Furthermore, in his more recent work, Bennhold stated that the migration of acid and basic dyes in serum goes in the same direction in the electric field. Under these conditions it is rather questionable whether the direction of migration in the electric field is concerned preponderantly with the disappearance time of dyes on intradermal injection of normal persons. It is still possible that among the various factors which determine the disappearing time of dyes, electric influences play a part

Hudack and McMaster stated that intradermal injections are predominantly intralymphatic Lymphatic capillaries in regions injured in valious ways are far more permeable than usual. Serum added to the vehicle retards the penetration of dye from the lymphatic structures to the interstitial spaces We added Congo ied and methylene blue to serum of man so that the concentration of the dye was approximately 0 01 100 This was done by adding 01 cc of 1 500 solution of dye to 2 c c of serum Under these circumstances the dye spread more easily and disappeared more quickly. For instance, in forty-eight hours, Congo red mixed with serum had entirely disap peared when injected into three subjects, whereas when mixed with physiologic serum it was still visible in seventy-two to ninety-six Methylene blue mixed with serum disappeared in twenty-four hours, while mixed with salt solution it could be seen from thirty-six These results are in accord with other expento seventy-two hours After intravenous injections of Congo red, the dye appears in the wheal produced by mechanical irritation of the skin or by intradermal injection of histamine or codeine,8 17 and it disappeared more rapidly than we expected from the intensity of the color

It is by no means certain that spreading in the lymphatic structures is the only factor concerned here—Bennhold has shown that different dyes dissolved in serum penetiate into gelatin to an equal distance in a given time, even if in watery solution they show great variations dependent laigely on the size of the particles

This difference may explain, at least partially, the slow disappearance time of Congo red in cases of edema in which the edema fluid

is poor in protein. In some children with nephrotic edema the color was distinctly visible after one to two weeks. The die did not spread as much as usual Congo red in serum seemed to disappear more rap idly, also, in cases of edoma. In a case of lymphedema of the right leg the dve disappeared in three days from both legs. So far the number of our observations with dies in various diseases is too small to permit consideration

Such tests may become useful, since it has been shown by Höber and Banus, Mond, Wertheimer, Keller, and others, that change of conditions may change the permeation of dyes in cells and membranes

#### CONCLUSIONS

The disappearance time of dyes injected into the superficial layers of the skin of normal persons does not seem dependent on their di rection of migration in the electric field. Neither can a definite dis tinction be made between acid and basic dyes. If ithin certain limits the degree of dispersion does not seem the deciding factor

Congo red and methylene blue dissolved in serum disappears more rapidly than when dissolved in salt solution

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# BODY BUILD IN INFANTS WITH ACUTE INTESTINAL INTOXICATION

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 $B^{Y}$  BODY build is meant the external form of the body as determined by the skeletal parts. No attempt will be made here to critically evaluate previous studies on this subject. It will suffice to state (1) that hitherto studies have been largely qualitative and have depended for the most part on subjective interpretations, and (2) that modern statistical methods for expressing and evaluating data have not been generally applied. Attempts have been made to describe body build in terms of indices, i.e., the proportion of one dimension to another, as the cephalic index  $\left\{\frac{\text{cephalic breadth} \times 100}{\text{cephalic length}}\right\}, \text{ the facial index}$  etc., but the indices hitherto used have

not yielded results of statistical reliability. The use of indices in children is complicated by the factor of growth which results in a continuous change in the relation of one dimension to another

In the present study the simple expedient of relating the various dimensions to total body length has been adopted. The value of this device will be apparent when the data are presented below

A difficulty in the study of body build is the choice of dimensions to be measured. Since qualitative studies of body build lay emphasis on "laterality" versus "linearity" in describing body configuration dimensions were chosen which measure this quality, i.e., the bimalar and bigomial diameters of the face, the biacromial and bicristal diameters of the trunk and the circumference of the chest at the nipples. These measurements are taken from bony points and hence errors due to nutritional status are minimal. A large number of other dimensions have also been measured but these have not yet been evaluated

The technic for making the measurements has been described in full elsewhere <sup>2</sup> The dimensions used in this paper were measured as follows

- 1. Diameter of face (bimalar) The horizontal distance between the two malar prominences
- 2 Bigonial diameter of face The horizontal distance between the most distant points of the angles of the jaw, perpendicular to the midsagittal plane
- 3 Biacromial diameter Straight distance between the most lateral points of the acromial eminences, taken from behind with the child seated, the arms close to the thorax.

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- 4 Bieristal diameter Straight distance between the most lateral points of the iliae crests, perpendicular to the midsagittal plane
- 5 Circumference of the chest at nipples. Taken halfway between inspiration and expiration. The respiratory excursion of the chest of a quiet infant is small

Measurements of the external dimensions of healthy infants were made in order to establish norms with which to compare sick infants. The group of well infants comprises abandoned infants, infants left in the hospital because of unsuitable home conditions, and infants ad mitted to the hospital with mild upper respiratory infections. There were 397 males and 347 females. The patients with acute intestinal intoxication, as well as the healthy infants, were from a poverty stricken group, and were measured shortly after admission to Bellevue Hospital.

In an earlier study the various measurements for all well infants under 1 year were recorded in relation to total body length and aver

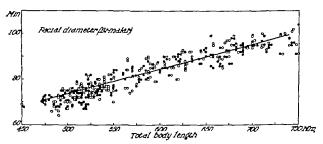


Chart 1.—The relation between total body length and the bimalar diameter of the face during the first year of life. Dots represent individual measurements on females, the circles on males. The continuous line is the curve of central tendency

ages and standard deviations calculated by various subdivisions of body length as illustrated in Chart 1 for the bimalar diameter of the face. A curve of growth for the body dimension in question, in relation to total body length, was then constructed by connecting the points representing the average values. Dimensions of the infants with acute intestinal intoxication were compared with these curves and the reliability of the differences tested statistically. These differences were found to be significant.

Since growth during the first year of life is rapid the rehability of grouping together all infants in this age period may be questioned Growth curves for the various lateral dimensions have been constructed therefore, for smaller subdivisions of age under 1 year and it is with these groups that the sick infants are here compared

Description of Clinical Material —Acute intestinal intoxication is here used to designate a type of reaction in infants characterized by

somnolence alternating with periods of hyperirritability, by acidotic hyperpnea and by evidence of dehydration. There is usually cyanosis and oliguria of anuria. Fever and an associated infection are frequently present and anorexia, vomiting and diarrhea are usual. Convulsions are occasionally observed. There are no characteristic gross anatomical changes, except, perhaps, in the liver

The cases were collected over a period of 3 years, for the most part during the winter months — The distribution of cases by season of the year is shown in Table I

TARLE T

	NUMBER OF CASES	PERCENTAGE OF DEATHS
January February	30	70
March April	41	73
May June	56	61
July August	19	47
September October	40	60
November December	34	53
	<del></del>	
All Months	220	62

There were 119 males and 101 females all of whom were under 1 year of age Sixty-two per cent of the infants died. Only children of Caucasian parents are included in this study since the body build of colored infants is known to be different. Sixty-two patients (28 per cent) were measured before the onset of acute intestinal intoxication.

Most of the infants showed evidence of upper respiratory infection In addition the following associated conditions, shown in Table II, were present

TABLE II

ASSOCIATED CONDITION	NUMBER OF CASES	ASSOCIATED CONDITION	NUMBER OF CASES
Mastorditis	1	Scurvy	1
Pneumonia	22	Tetany	1
Eczema	5	Peritonitis	1
Erysipelas	1 1	Pylorospasm	2
Pyuria	4	Prematurity	3
Emypema	1	Total	42

In Chart 2 the height of infants with acute intestinal intoxication (dotted line) is compared with the height of the healthy infants (continuous line) from the same social environment. The averages for the sick infants are regularly below those for the healthy

In Charts 3, 4, 5 and 6 the lateral dimensions of infants with acute intestinal intoxication, represented by dots, are compared with the healthy, in relation to body length, for various subdivisions of age under one year. Continuous lines represent the average values for

healthy infants. The dotted lines represent one standard deviation on each side of the average and include 68 per cent of the healthy infants. Data are shown only for the first 24 weeks of life. The number of cases after this age period was too small to be of significance.

Dimensions of the infants with acute intestinal intoxication tend to fall below the average lines for the healthy indicating that infants with acute intestinal intoxication are relatively smaller in their lateral dimensions than are the healthy infants. No difference was found for the bicristal diameter of the trunk in the present enlarged series or in the series previously reported.

Infants measured while well, who subsequently developed acute intestinal intoxication showed the same body configuration as the infants measured when ill and are included with the sick infants. The infants with acute intestinal intoxication who died showed no differences from those who survived



Chart 2.—Comparison of the total body length of health; infants (continuous line) and infants with acute intestinal intoxication (dotted line)

The relative narrowness of infants with acute intestinal intoxication is not characteristic of all sick infants. As has been previously shown in infants with tetany and in infants with eczema the lateral dimensions are relatively larger than in the healthy infant.

A rational basis for the difference in the body build of infants with acute intestinal intoxication may be deduced from a comparison of the growth of two groups of healthy infants from different social environments. In addition to the healthy group already described, a scries was studied in a 'well baby' clinic at the Fifth Avenue Hos pital. The infants were derived from families of moderate income and were observed from birth through the first year. The racial make up of the two healthy groups was similar and has been shown to be without influence on the dimensions measured.

It was found that the infants in the well baby clinic group were superior both in weight and height to the healthy infants in the poverty group. It was also found that, for various subdivisions of age, the poverty group infants were smaller in their lateral dimensions than were those from the well baby clinic

From these results it may be stated that, when in a group of infants, a delay in growth occurs, the delay is more marked for the lateral dimensions than for the cephalocaudal There results, on the one hand, a change in body build, the delayed group becoming relatively smaller in their lateral dimensions, and, on the other hand, a

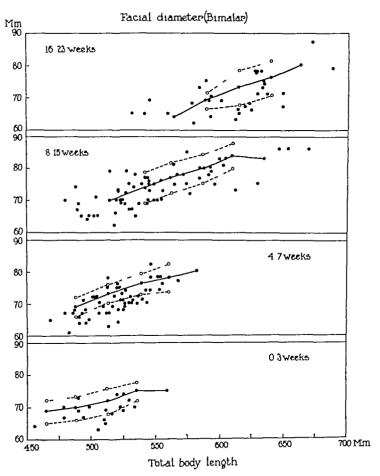


Chart 3—The relative width of the face (bimalar diameter) in infants with acute intestinal intoxication. Continuous lines connect the average values for healthy infants Dotted lines represent one standard deviation on either side of the average Dots represent infants with acute intestinal intoxication

susceptibility to the development of acute intestinal intoxication. It has long been known to pediatrists that when a retardation of growth occurs in infants, all parts of the organism are not equally involved, the delay in growth of weight being more striking than the delay in growth of height. The infants with acute intestinal intoxication were compared with the Bellevue Hospital group, itself a delayed group

Had the comparison been made with the "well baby clinic" group the differences would have been much more marked

About 18 months ago a well baby clinic was established in the poverty district. Only infants born in Bellevie Hospital were treated. The incomes of the families were similar to those of children in the hospital group. The results of this study will shortly be published in detail. It may be here stated that the values for the well baby clinic at Bellevie Hospital were identical with those obtained in the well

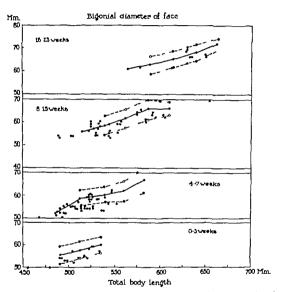


Chart 4—The relative diameter at the angle of the jaws (bigonial diameter) in in fants with acute intestinal intoxication.

baby clinic at the Fifth Avenue Hospital the Bellevue district group growing as well in height and weight and having the same body proportions as the Fifth Avenue Hospital group

The relation of deficient diet to the attology of acute intestinal intoxication. Acute intestinal intoxication tends to occur in infants who are shorter and relatively smaller in their lateral dimensions than are healthy infants. That this type of body build results, in part, from environmental influences is borne out by the two groups of studies mentioned above i.e. (1) the differences in body build of two groups

of healthy infants of similar lacial make-up but from different social environments, and (2) the change in body build in a group of healthy infants from a poverty-stricken environment following the institution of a health clinic. It seems reasonable to assume that the prominent environmental factor introduced by the health clinic was diet. Whether acute intestinal intoxication results from inadequacy in the

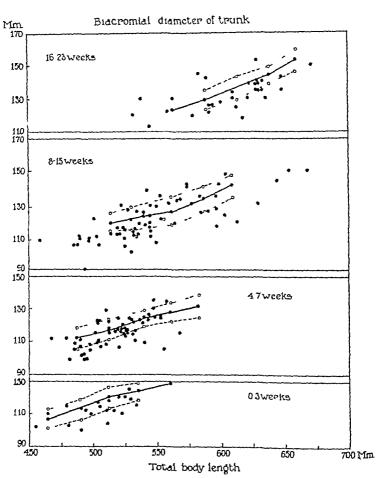


Chart 5 - The relative width of the shoulders (biacromial diameter) in infants with acute intestinal intextication

amount of energy-producing substances in the diet or from a deficiency in a specific food factor cannot be stated

Infants with the growth changes herein described, when exposed to infection (as occurs frequently during the winter months) or to high external temperatures (during the summer months), react with the disease syndrome known as acute intestinal intoxication. In this respect there is a close analogy to tetany which is equent until made manifest by an infection

The mechanism by which a dietary inadequacy leads to acute in testinal intoxication is as obscure as the mechanism by which any of the known vitamin deficiencies lead to disease

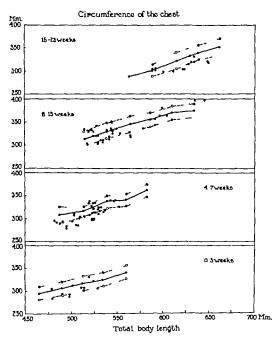


Chart 6 -The relative circumference of the chest in infants with acute intestinal intextinal

#### SUMMARY

- 1 Infants with acute intestinal intoxication are, on the average shorter than healthy infants from the same social environment
- 2 In relation to total body length, infants with acute intestinal in toxication have narrower faces, narrower shoulders and smaller chests than healthy infants
- 3 The proportion of the dimensions mentioned above to total body length in infants with acute intestinal intoxication is determined, in part by a retardation of growth

4 Since deficient diet leads to retardation of growth, it is reasonable to look upon acute intestinal intoxication as causally related to dietary deficiency

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132 EAST SEVENTY FIRST STREET

#### ACRODYNIA

### A NOTE ON THE PATHOLOGIC PHYSIOLOGY

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THE clinical syndrome which is now called acrodynia, although first described in 1903, escaped attention until recent years, when it was recognized independently in widely separated geographical locations and designated by a number of descriptive titles. Among the names which have been used to designate this bizarre condition, some at least should be mentioned.

Trophodermatoneurosis (Selter) 1903
Erythroedema (Swift) 1914
Swift's disease
Pink disease (Clubb)
Acrodynia (Weston) 1920
Polyneuritic syndrome resembling pellagra (Byfield) 1920
Vegetative neurosis (Feer) 1923
Feer's disease (Erickson)
Dermatopolyneuritis (Thursfield)

The first series of cases to receive prominence was that reported by Swift in 1914. Not until 1920 were descriptions of the disorder published in the United States. Following the reports by Bilderback, Weston' and Byfield, references to this apparently new disease appeared in the literature in rapid succession.

In Europe the first descriptions appeared in the literature in 1921. Among the many contributions to this subject in the years of recognition and definition, the careful observations and added information concerning the disease contained in the studies of Feer in 1922, and subsequently, mark these papers as of outstanding importance. However, the conception of this author of the pathogenesis did not immediately receive widespread acceptance.

As in any recently described disease, the typical severe example has become readily recognized, but only in the light of accumulated ob-

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References to acrodynia in the literature exceed 150 available articles of which 40 or more were published in this country. It is manifestly impossible in a short note to review the literature in any detail and to give adequate credit to authors for priority as regards descriptions of features of the clinical picture of the disease.

servation and experience are the variations in the clinical picture, and particularly the mild and borderline cases, clearly defined. It is the purpose in this paper to consider briefly certain features of acrodynia as observed in a series of forty-four cases seen in this clinic within the past nine years, and to correlate so far as permissible the clinical manifestations of the disease with the pathologic physiology.

Acrodynia is a disorder, encountered in infants and young children, of gradual onset, and prolonged course, with a characteristic train of symptoms which, however, may vary considerably in intensity. Unless terminated by an intercurrent infection, the outcome is usually favorable. Frequently the mother cannot state accurately the time of onset of the disease although in many instances an upper respiratory infection either initiates the symptoms or quickly becomes an associated

TABLE I
FIRST SYMPTOMS OBSERVED BY INFORMANT

SYMPTOMS	NUMBER OF PATIENTS	
Fatigue, irritability, anorexia	17	
Lacrimation and photophobia	5	
Painful and itching extremities	6	
Rash (erythema on face and body)	5	
Deep muscle pain	3	
Pain in abdomen	3	
Vomiting	1	
Furunculosis	1	
Enurems	1	
Convulsions	1	
Loss of weight	1	
Preceded by acute respiratory infection	12	
No acute infection noted preceding onset	32	

The infant or young child gradually becomes irritable, fretful and sleepless, and refuses food Cessation of growth and then progressive loss of weight ensue Profuse sweating, lacrimation and photophobia with excessive secretions from the nose and throat develop The cheeks are bluish red in color, with the tip of the nose, in many cases, very red The expression of the suffering patient is Ulcerations of the mucous membrane of the worried and unhappy mouth are of frequent occurrence Sooner or later hyperemia alternating with ischemia appears on the hands and feet. The palms and soles develop a dull, beefy red, frost-bitten appearance, and although infants show evidence of marked discomfort and older children complain of intense burning and itching in these locations, the extremities usually feel cold and clammy Maceration of the skin of the palms and soles occurs followed by desquamation and frequently secondary infection Rashes of papular type which itch intensely may appear over the whole body There is, however, a wide variation in the intensity or severity of the cutaneous lesions and it seems quite possible that a patient may suffer from acrodynia and present minimal

skin lesions Falling out of the hair loosening of the teeth, loss of finger and too nails are frequently observed

The patient tends to assume abnormal positions in bed, frequently placing himself in the knee-chest position with his head burrowed in the pillows. This position has been attributed to the photophobia, but, as older children with the disease often complain of abdominal cramps, we are inclined to believe that even infants may assume this position in an attempt to relieve abdominal discomfort.

Physical examination reveals fundamental circulatory disturbances early in the disease, often before the appearance on the hands and feet of the typical vascular changes Signs of the circulatory involvement are tachycardia and an elevation of the blood pressure. The pulse rate varies usually between 140 and 200 per minute and is little influenced by cry effort or sleep. The rhythm is regular. The appearance of tachycardia in the early course of the disease is well illustrated by the following case A little girl of five and a half years, who was brought to her physician because of anorexia was found to have a persistent tachycardia without other physical signs of disease quently, after a period of several weeks, the typical manifestations of acrodynia developed Hypertension is present to some degree in all cases and is said by Feer to be the most constant sign of the disease In another of our patients, a boy of seven years, abdominal pain, hy pertension and tachycardia preceded by several weeks the appearance of cutaneous manifestations Electrocardiographic tracings show no abnormality other than tachycardia

In addition to the features mentioned above symptoms referable to the central nervous system with profound mental disturbances frequently appear early and persist throughout the course of the disease Lassitude apathy irritability and disturbances of the sleep rhythm together with diminished activity and muscular hypotonia are almost constant findings. Muscle pains are complained of and weakness or paralysis of the extremities occur occasionally. In one of our patients presenting a typical picture of acrodynia, paralysis of the extremities developed with loss of deep reflexes and persisted for three weeks with thereafter a gradual return to normal function throughout this period sensation in the extremities remained intact. It is not unusual for the patients to develop tremors of the extremities and even coma and convulsions. We have observed four patients with convulsive episodes.

As mentioned previously evidences of an increased secretory activity become manifest. There is excessive lacrimation and rhinorrhea sialorrhea and sudoresis. Dehydration evidently is due in addition to the diminished fluid intake to water loss through the skin resulting from the glandular activity.

Anorexia, vomiting, and constipation are among the evidences of gastrointestinal disturbance commonly observed in acrodynia Analysis of the gastric contents in two of our patients showed achlorhydria, there was, however, a normal response of gastric secretion to histamine

Our analysis did not show with any constancy the elevation of the basal metabolic rate which has been described in the disease. Although the basal metabolic rate was found in one case to be as high as 60 per cent above normal, in other patients dependable determinations of the metabolism showed a normal or even reduced oxygen consumption. The difficulty in establishing basal conditions for the determination of the metabolic rate is obvious in children who are fretful, irritable and suffering from constant pain

The percentage of sugar in the blood was frequently abnormally high and glucose tolerance tests showed, in five of six cases, curves simulating in some respects those found in patients with diabetes

The urine of patients in the more severe stages of acrodynia has been usually quite concentrated, probably due to the partial dehydration of the patients Albumin was found in the urine on one or more occasions in ten of our cases Glycosuria was even more frequent, occurring in fourteen patients

Erythrocytosis and leucocytosis were present in the peripheral blood, due probably to the partial dehydration mentioned above. An elevation of the serum protein was found to be present in some cases and absent in others. In one instance the serum protein was reduced to 45 gm per cent, although the child had a polycythemia and other evidences of mild dehydration. The failure of the serum protein to be elevated in this and similar cases was thought to be due to the prolonged partial starvation of the patient with considerable destruction of tissue proteins and ultimate reduction in the serum protein

The inorganic elements of the blood of patients suffering from acrodynia have been depicted as within normal limits, with the exception of the blood calcium which has been reported to be elevated <sup>8</sup> Remarkable elevation of the blood calcium was not found in our experience, nor were there reductions below the usual normal figure

The etiology and pathogenesis of acrodynia remain obscure despite efforts on the part of numerous investigators to east some light on the subject. Two possible underlying causes of the disease have been suggested, infection and dietary deficiency. Unequivocal supportive evidence for one or the other of these causes was not found in our analysis nor from observations secured by various therapeutic tests. In this connection, however, it is of interest to note the seasonal incidence according to the time of hospitalization of the patients in this series of cases (Fig. 1). When the presenting symptoms, the physical signs and the laboratory data are considered carefully, it is apparent that there is present a widespread and fundamental derangement involving

many organs and tissues of the body Therefore, it does not seem un reasonable, whatever the precipitating cause, to relate certain of the outstanding features of the disease to disturbance of the central nerv ous system together with a dysfunction of the autonomic nervous system, the latter suggested first by Feer

Mentioned briefly, the signs which in our opinion are indicative of dysfunction of the autonomic nervous system are dilatation of the pupil and photophobia, rhinorrhea, sialorrhea and sudoresis, vaso motor disturbances of peripheral vessels of the hands and feet, tachy cardia and hypertension, alopecia neurotica, spasmodic abdominal pain, hyperglycemia and increased basal metabolic rate

Inasmuch as contraction of the spleen is brought about through the activity of the sympathetic nervous system splenic enlargement

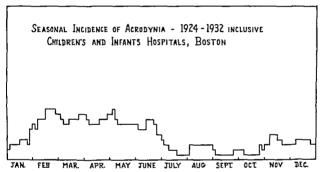


Fig 1.—This figure is constructed from hospital patient days and represents the autumation of the periods of hospitalization of our cases. Obviously the onset of the disease precedes by an indeterminable period the peak shown in the figure.

should be encountered but rarely in a disease characterized by excessive activity of this system. It is interesting to note that in only one of our forty four cases was the spleen enlarged. In this patient the spleen was readily palpable in the early stages of the disease but within a few weeks it became reduced in size so that it could no longer be felt.

In Table II are listed the outstanding symptoms and signs of acro dyma compiled from the literature and confirmed by the analysis of our series of cases. The features of the disease are shown in relation to the known action of various portions of the nervous system Many of the symptoms and signs suggest definitely a cerebral involvement and others point to a spinal cord or peripheral nerve injury Numerically, however the manifestations are predominatingly those of a disorder of the autonomic system

# TABLE II

# PATHOGENESIS OF THE SYMPTOMS AND SIGNS OF ACRODYNIA

I Symptoms of cerebral or spinal involvement

Apathy

Muscular weakness and paralysis

Deep muscle pains

II Symptoms probably cerebral or spinal but possibly due to autonomic involvement

Hypomotility and hypotonia

Hyperesthesia

Coma and convulsions

III Autonomic involvement

Sympathetic disturbances (overactivity)

Vasomotor disturbance (hands and feet, less marked on trunk)

Dilatation of the pupil and photophobia

Tachycardia

Sweating

Falling of the hair

Hypertension

Elevated blood sugar-glycosuria

Autonomic disturbance, not definitely assignable to sympa thetic involvement and possibly due to parasympa

thetic involvement

Salivation

Rhinorrhea

Vomiting

Abdominal pain

Hypomotility alternating with colicky hypermotility

of G L tract

Constinution

Difficult micturation

IV Secondary involvement

Maceration of skin due to profuse sweating

Secondary infection

Dehydration due to excessive water loss

Elevated red cell count

Elevated serum protein

Concentrated urine

Constipation

Loss of weight

Negative nitrogen balance

In Fig 2 is shown a chart of the relationship of the autonomic nervous system to the innervation of the organs and tissues of the body Apparently not only the thoracoabdominal autonomic, the sympathetic system, is involved in acrodynia, but there is also a disturbance of the craniosacral, or parasympathetic system. Inasmuch as the sympathetic and parasympathetic nervous systems have opposing actions in those organs where fibers from both enter into the nerve supply, it is

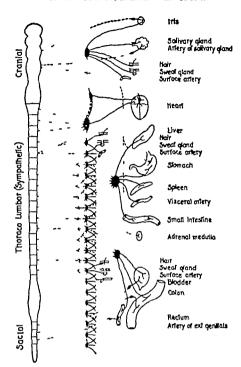


Fig. ... Diagram of the general arrangement of the autonomic nervous system.

The brain and spinal cord are represented at the left. The norces of the somatic system are not shown. The pregangitonic fibers are in broken lines, the poet ganglionic fibers are in solid lines. The craindi and search autonomic systems have limited, sharply directed, nervous discharges to specific organs, while the sympathetic has a directed discharge of impulses by reason of the extensive bridging or connecting fibres overlapping one another and reaching some distance up and down the chain of ganglia.

The outstanding functions of the autonomic nervous system may be listed as follows

Cranial Autonomic

- 4 secretory to glands of stomack. 5 secretory to paratid gland. 6 constriction of pupil. 1 depresses and slows the heart. 2. constricts bronchi.
- s motor to intestine-relaxation of aphincters
- i contraction of muscles of bladder 2. erection of penis by relaxing walls. 3 motor to large intestine.

#### Sympathetic

- mpaneus

  1. dilatation of pupil

  2 secretory to speed gland

  2 con-constrictors with few dilator
  fibers to blood ressels.

  4 acceleration and increased contraction
- of keart
- dilatation of bronchi, inhibition of bladder contraction, contraction of bladder sphincler contraction of spicen.
- increased conversion of glycopen into glucose in liver
- (Figure reproduced through the courtesy of Dr W B. Cannon, from his book The Wisdom of the Body W W Norton and Company Inc. publish rs.)

manifestly impossible in considering many of the features of acrodynia to determine whether the imbalance of control with the resulting overactivity of an organ is the result of increased stimulus from the one system or diminished and suppressed activity of the opposing system

Finally, certain features of the disease may be considered to be due to alterations in body function entirely secondary to one or another of the underlying disturbances. The manifestations which may be considered secondary have been so listed in Table II.

From a study of Table II it becomes apparent that the outstanding features of acrodynia may be attributed to overactivity or unopposed activity of the sympathetic nervous system. Dehydration, partial starvation and secondary infections account for many more of the symptoms observed in the condition. But there still remain a number of manifestations which point definitely to a central nervous system involvement.

The number of organs and tissues involved in acrodynia with clinical manifestations referable to a central nervous system disorder together with an extensive involvement of the autonomic nervous system would suggest, if this conception is true, that pathologically there should be found in acrodynia a widespread peripheral lesion involving the sympathetic chains or a central lesion involving particularly the region of the centers of autonomic control, which are presumed to be located in the diencephalon. The central lesion would more satisfactorily explain the complete picture

Clinical pathologic data supporting the conception of a central nervous system involvement are found in examination of the spinal fluid Early in the course of the disease the spinal fluid has been reported to show an increase in globulin and a pleocytosis 8 Spinal fluid examinations were made on one or more occasions in seventeen of our patients None of these examinations were made at the onset of the disease inasmuch as hospitalization of the patients was not carried out until the process had become quite advanced Our analysis showed the spinal fluid to be under normal pressure and to be clear and colorless cell counts were within normal limits The globulin was increased as determined by the Pandy test in six of the seventeen cases, and quantitative determination of the total protein yielded values as high as 250 mg per 100 c c of spinal fluid. The sugar was normal in nine cases and appeared to be abnormally high in the remaining eight cases These findings in the spinal fluid would not indicate the presence in the brain of hemorrhage or gross inflammation The increase in the total protein, however, might well indicate a mild inflammatory or a degenerative process

With these possibilities in mind, pathologic changes in acrodynia should be sought in the central nervous system, and in the sympa-

thetic chains Such searches have not been entirely unrewarded. De generative changes in the myelin sheaths of the peripheral nerves have been found by several investigators. However, degenerative changes per se do not indicate the position of fundamental pathologic changes but only that they may be higher up. In fact, degenerative peripheral changes are found in a variety of diseases with central nervous system lesions, among them poliomyelitis and various forms of encephalitis.

Pathologic material secured from patients with aerodynia is not extensive, but various studies, apparently thoroughly made have shown that in aerodynia, in addition to the degenerative peripheral demyelinization, cellular infiltration is present in the spinal cord and in the nerve roots. Byfield early reported degenerative changes in the anterior horns of the spinal cord, edema of the sensory roots and beginning degeneration of the nerves. Paterson and Greenfield refer to cellular infiltration in the spinal cord, with demyelinization of the peripheral nerves. Kernohan and Kennedy have described extensive demyelinization as well as degeneration in the spinal cord extending as high as the base of the brain

Warthin<sup>12</sup> found in two cases of aerodynia the essential pathological changes to be extreme edema and slight meningeal irritation of the central nervous system, chronic crythema of the skin with hyper keratosis hypertrophy of the epidermis and sweat glands with slight pigmentation of the rete, with associated or terminal respiratory in fections and gastrointestinal "entarth and manution".

Wyllie and Stern<sup>13</sup> confirmed the finding of diffuse infiltration of the spinal cord described first by Paterson and Greenfield, but were unable to determine the type of infiltrating cells. Chromotolysis of the central type was found in the anterior horn and myelin degeneration was observed in the peripheral nerves

Orton and Bender<sup>14</sup> found chronic lesions in the lateral horns in the thoracic and lumbar regions loss of nerve cells, with glial replacement. The cells which were lost were the ones which are said to connect the spinal cord with the sympathetic nervous system.

Careful serial sections of the brain stem thus far have yielded alight additional information. De Langer made serial sections of the di and mesencephalon and found in the regio tuberoinfundibularis both diffuse glial proliferation and small glial nodules. There was no neuronephagia. Here and there in scattered, irregular distribution there was slight glial proliferation in the basal ganglia, thalamus, and den tate nucleus.

From a study of five cases of acrodynia at autopsy we have been unable to demonstrate histopathologic changes which could be con sidered characteristic or explanatory of the disease. All of the deaths in this series were attributable to severe acute infections mainly in the upper respiratory tract and lungs. The changes in the other or

gans could be explained largely on the basis of the terminal infec Examination of the central nervous system, the peripheral nerves and the sympathetic nervous system failed to disclose micro scopic changes which could not be related to the terminal infection

# SUMMARY

The data herein reviewed support the suggestion that the manifestations of acrodynia are dependent upon a diffuse disorder of the central nervous system with associated involvement of the autonomic nervous system The mechanism by which the symptoms and physical signs of acrodynia are produced is, in large measure, traceable to a diffuse stimulation of the autonomic nervous system with involvement and overactivity not only of the sympathetic but also of the parasympathetic divisions of this system

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# THE ROLE OF ERITHROCYTE FRAGMENTATION IN THE GENESIS OF ANEMIA

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FRAGMENTATION with ultimate disposal of the fragments by phagocytes of endothelial origin, has long been recognized as the normal method of disposal of the red cell. Ehrlich, as long ago as 1880, described the process in some detail, recognizing the polkilocyte as a cell preparing for dissolution and designating the free motile fragments seen in fresh preparations as schizocytes. A number of other observers commented on evidences of fragmentation seen in normal blood and the common assumption seems to have been that these fragments grow smaller and smaller through the mechanical effects of attrition in the circulation, to become a sort of hemoglobin containing dust whose final disposition is a function of reticuloendo thehum in various sites. Rous and Robertson in 1917 published observations which went to prove that fragmentation is a constant feature of the blood of normal animals. Rous in 1923 reviewed the whole literature of the normal fate of the red cell and Doan and Sabin in 1926 gave a rather more complete description than any of the others of the fragmentation as seen in rabbits blood, with obser vations also on ultimate phagocytosis of the fragments by desqua mated endothelial cells in the blood stream

From these studies we obtain a very satisfactory picture of what happens to the senile red cell up to the final, still little understood process of biliruhin formation and reutilization or deposition of the iron. The fragmentation process is best studied in the fresh moist preparation unstained or made with a film of neutral red scaled with a mixture of vascline and paraffin and watched in the warm box whose temperature should be kept below 37°, as above this point increases in temperature have been observed to cause acceleration of the process (Isancs Doan and Sabin and others) We can offer no better description of what is to be seen in the sealed film of normal blood than that of Doan and Sabin, which we quote "In watching fragmentation we have found that a red cell puts out a long process and thereby becomes the so-called polkolocyte. At first the process does not move then it begins to vibrate slowly then faster and faster This vibration marks the beginning of fragmentation. As the proc css vibrates it gradually becomes thinner and thinner at some point and then separates. If the thinned out place is at the end of the long process the fragment becomes a rod often looking like an irregu

lar but yellow bacillus, if near the tip, it becomes a round or oval body. We have seen every variation in size and shape of these processes, up to an actual division of a red cell into two equal parts. Sometimes two or more processes form on a red cell at the same time." We would add to this an observation of our own, made also by Ehrlich, that many of the small slender fragments, which are likely to have a refractile enlargement at one end, and to show a resemblance to spermatozoa, have definite independent motion, so that in the pathologic states to be described, in which the drop of blood is full of the fragments, one might easily think that he was observing the blood of some protozoan infection. It is, of course, to be understood that in normal blood comparatively few cells undergo disintegration at the same time, so that some search is necessary to find the fragmenting forms. We have found "budding" a convenient term for these cells that are putting out processes preparatory to fragmentation

Considering that it has been generally, if rather vaguely recognized that fragmentation plays the most important part in the normal destruction of the red cell, it seems surprising that so little attention has been given to the likelihood of abnormal increase in this process as a factor in the genesis of anemia. It is common enough to speak of "increased blood destruction" in certain types of anemia, but this increased destruction is more often a deduction from increased pigment metabolism, or from lack of other adequate explanation for the anemia than a direct observation, and the assumption is often made that increased destruction and "hemolysis" are synonymous terms Hemolysis should mean the freeing of the pigment from the red cell, as it may be observed in vitio as the result of certain immune reactions, exposure to chemical or bacterial poisons, or to changes in osmotic pressure, as in the fragility test In vivo such processes are They are to be met with in paroxysmal hemoglobinuma, in transfusion reactions and in some kinds of poisoning. The type of the so called hemolytic anemias is hemolytic icterus, in which the cells, which have a peculiar susceptibility, apparently collect in the spleen and lose their pigment there by a process not clearly understood, but which is not preceded by fragmentation in the blood stream Erythroblastosis fetalis probably involves a similar process of the anemias often spoken of as hemolytic, however, including pernicious anemia, erythroblastic anemia, perhaps sickle cell anemia and the hemolytic anemia of piegnancy, probably do not belong in this Hemolysis as observed in vitio involves the passing of the hemoglobin into solution in the fluid menstruum, with the cell form remaining as a "ghost". The breaking of the cell into pieces which retain their hemoglobin evidently should not be confused with this, even though hemolysis must be the ultimate fate of this hemoglobin

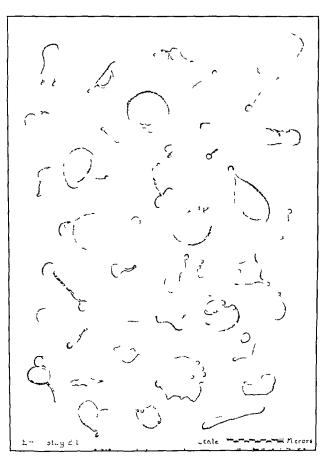


Fig. 1.—Fragments and forms of cells about to break up as seen in the sealed fresh film.

Our attention was first called to the clinical significance of excessive fragmentation in the case of a four-year-old gul admitted to the Children's Hospital in November, 1932, because of jaundice, ascites and splenomegaly which had developed in the course of chronic suppurative of other Splenectomy was necessary, and the spleen showed an extreme degree of chronic infectious splenitis. The jaundice and ascites disappeared after the operation and have not returned

The patient was not anemic on admission, having 135 gm Hgb and 4,600,000 RBC There was, however, evidence of considerable disturbance in erythropoiesis, with anisocytosis and polkilocytosis, many microcytes, and 10 per cent reticulocytes. Resistance to hemolysis was somewhat increased, and the curve of gastric acidity was normal. Quite exhaustive laboratory studies gave no other significant findings.

The child did well until, in the course of convalescence, suppuration developed in the operation wound and in a needle puncture This was followed by a rapid fall in hemoglobin and erythrocyte count, which soon produced a state of grave anemia Studying the blood at this stage, Lee was struck by the numbers of peculiarly shaped erythrocytes, whose development she thought would be better observed in moist preparations. These were made, and presented a remarkable picture The whole film was alive with motile, hemoglobin-containing fragments the commonest being the spermatozoonlike forms already mentioned A large proportion of all the red cells showed some one of the forms of distortion described by Doan and Sabin as preparatory for fragmentation, either the polkilocyte with the waving tip, the slender processes, single or multiple, or the nearly median fission, the latter being obviously the cause of the many microcytes to be seen in the film. It was evident that a large proportion of the erythrocytes were being destroyed at the same time, and that regeneration was not keeping pace with this process, as few young This destruction was not due to any toxic forms were to be found property of the serum, as cells from a normal person mixed with the patient's serum were not affected, nor did the patient's cells disintegrate less rapidly in normal serum. After a few days' study of these phenomena transfusion became necessary Other therapy was not employed as it was desired to observe the behavior of the trans The immediate effect of transfusion was striking child, previously prostrated and apathetic, revived immediately, and The transfused cells were evidently not was happy and playful affected by the fragmentation process, as the proportion of distorted cells was greatly diminished and remained so for more than two weeks, as might have been expected from the normal life of the transfused cells, with the patient's cells undergoing destruction as before Our observations were interrupted at this point by an attack of

measles On her return two weeks later she had only 25 gm Hgb, with no important change in the rest of her blood picture except that there were 900,000 platelets and 17 per cent normoblasts Reticulceytes were absent Fiagmentation was again extreme Transfusion was followed by the same response as before

We have observed this sequence of events in this patient after four Each time there has been the same prompt improve transfusions ment, with marked diminution of degenerating cells, which lasts be tween two and three weeks, after which the great excess of fragment ing cells is again apparent. In all this time there have been practi cally no reticulocytes in the blood. The platelet count reached the maximum of 900 000 four months after the splenectomy then fell quite rapidly to the pre-operation level of 250 000. It did not appear to have any relation to the number of fragments in the blood. The patient has had during the period of observation operations upon both mastoids and a tonsillectomy. She had received liver aron and cop per for three weeks before the fifth (recent) transfusion without apparent effect upon the blood. Since this transfusion and the tonsil lectomy which followed it reticulocytes have reappeared in a pro portion of 10 per cent

We are satisfied that this whole disease picture has resulted from the toxemia of focal infection. The excessive fragmentation was probably beginning when she was admitted but was compensated by increased production until the wound infections added the final insult to the marrow. Since that time we have had a picture of hypoplasia of crythropoictic marrow plus greatly increased destruction by fragmentation. Our observations of the process of disintegration in the moist films and of the effects of transfusion have aided us greatly in understanding the genesis of the anemia. The splenomegaly had no causative part, but the splenectomy doubtless made the fragments more prominent in the blood stream through lessened phagoovtosis. Therapy if successful at all in such a case will probably help only after the patient is free of her various infections.

Three patients with crythroblastic anemia two of them sisters all of whom have had their spleens removed have been studied during this same period. This anemia is characterized by extreme hyper plasia of crythropoietic marrow and a constant outpouring of young and immature cells into the circulation with very high counts of reticulo cytes and crythroblasts. Increased pigmentation of the serum indicates abnormal destruction which we had supposed to be due to hemolysis of some type in spite of increased resistance to hypotomic solutions until we studied most films from these patients. They show the most extreme fragmentation that we have observed even when the hemoglobin and red cell levels are practically stationary. The balance is of course, due to the great increase in crythropoiesis. The

fragmenting cells show all the forms previously described, and in ad dition many which look as though they had been burst by an explosion. We have on various occasions tested serum from patients with this disease against normal cells without seeing any destructive effect. The great splenic enlargement is probably "spodogenous," and has nothing to do with causing the anemia

A boy of eight and one-half years, with a hypochromic, hypochlorhydric anemia said to have existed from infancy, gave interesting findings From the appearance of stained smears his anemia would have been termed microcvtic Fresh films gave a different impression There was decided excess of fragmentation, but of a somewhat different type from that observed in the first case, with fewer polkilocytes and "budding" cells, and a notable proportion of long elliptical cells resembling forms seen in sickle cell anemia These and many of the normal-sized round cells tended to divide by median fission, producing microcytes Our impression was that most if not all of the microcytes were produced in this way, and that the anemia could not be called microcytic in the sense that the small cells were produced by the marrow This blood was studied in an overheated box. Under this condition the process of fission could be seen to go on in a cell until there was a group of five or more minute round forms in the place of the original cell Ponder in his book describes precisely such an appearance as an evidence of hemolysis If he were night, there should be a ghost cell remaining, which we did not see There were less of the small fragments in this blood than in the bloods of the splenectomized patients, presumably because this boy's spleen was functioning

These were unusual types of anemia In attempting to estimate the general importance of fragmentation as a factor in producing anemia we have studied films from a number of the more ordinary This group has included (1) Three cases of the combination of deficient or improper feeding and infection so frequently seen in the polyclime They showed fairly severe anemias of the type analyzed last year by Josephs, in which he demonstrated increased destruction by determination of pigment excretion Hypoplasia of the erythropoietic marrow is unquestionably present in cases of this type In all these we were able to observe marked increase in the percentage of fragmenting forms, though the small fragments, more frequent than in normal blood, were not nearly so much in evidence as in the blood of the splenectomized patients (2) Two infants with streptococcus septicemia In one, with hepatitis and jaundice, but little anemia, we could not detect increased fragmentation, in the other, without jaundice but more anemic, it was definite (3) Three cases of pneumonia In two, with moderate anemia, we could not definitely see an increase in fragmenting forms, in the third, a more anemic

infant in whom malnutrition had probably played a part, it was very distinct (4) A severe anemia in a three months old infant of the type which we have described elsewhere as due chiefly to deficient iron reserve, with the acute development precipitated by infection. This blood showed many misshapen forms but few small fragments. Within a few days after a transfusion all signs of cell destruction had disappeared. In the cases which responded with moderate rapidity to medical treatment signs of fragmentation progressively diminished but this did not always seem to keep pace with the clinical improvement, nor was there any obvious relationship between the appearance of reticulocytes and the disappearance of fragmentation

Recently we have had in the hospital two sisters with congenital hemolytic ieterus. One came in just after a hemolytic crisis, and the second was admitted during a crisis in which her hemoglobin fell from 15 gm to 6 gm within ten days. Neither of these patients showed any sign whatever of cell disintegration in the circulating blood. It was noticeable that the moist films seemed to show less microcytosis than the stained smears, also that there were no polkilocytes in stained preparations.

#### DISCUSSION

Study of the red cells in fresh sealed preparations was once a common precedure. Of recent years staining methods have almost en tirely supplanted it except in the diagnosis of sickle cell anemia, and in the "supra vital" technic. Our studies on these cases have led us to believe that it still has a very definite place in the appreciation of the mechanism of anemia. We have made use of the warm box at temperatures varying from 32° to 37° but it is not really necessary except for prolonged observation as the phenomena are readily observed at room temperature.

Our studies made in this way have satisfied us that in the ordinary secondary anemias and some of the primary forms blood destruction by an exaggeration of the normal process of fragmentation is a definite, easily observed feature, usually accompanied by indications of marrow hypoplasia in that regenerative forms are lacking. We have not arrived at a quantitative method of measuring fragmentation or the steps leading to it, but the difference between what is to be seen in normal blood and the appearance in a pronounced anemia are so marked that it is not difficult with a little experience to arrive at a fairly satisfactory standard of comparison.

The reason for this destruction is not perfectly clear. The natural assumption would be that the red cells which go to pieces so easily do so because of imperfect structure. Another possibility has occurred to us. If one thinks of the emergence of the cell into the circulation as a result of the push of new cells forming behind it, it might be

supposed that in a hypoplastic state the cells remain a longer time in the marrow, and are already old when they emerge. This obviously could not be the explanation of the destruction in erythroblastic anemia, in which an excessive output of young cells is a prominent feature. There is no good explanation of the abnormal fragmentation in this disease except defective structure. If the idea of old cells coming into the circulation in the hypoplastic states were accepted, it would explain such observations as the lack of marked increase of fragmentation in the early stage of the anemia, and its continuance after improvement has begun

The two cases of hemolytic icterus, as has been pointed out, give an entirely different appearance in the moist films. There is no indication here of fragmentation, and the microcytes, which are an important characteristic, are probably formed as such in the marrow, not the result of division in the blood stream. Polkilocytosis, which we believe to be evidence of fragmentation, is not, in our experience, met with in hemolytic icterus, although we have seen it noted in case reports. It is not impossible that in some cases both means of destruction might be at work, and this might explain the occasional failure of splenectomy.

We have had recently no case of sickle cell anemia in which the process was active. These cells would be difficult to study for fragmentation because of the rapid "sickling". This is generally assumed to be a hemolytic disorder, largely because of its resemblance in some features to hemolytic reterus. We are inclined to think that the resemblance to erythroblastic anemia is closer, and are not convinced that the disease belongs in the hemolytic group. This question might be settled by study of an appropriate case, especially after splenectomy.

Study of fragmentation might seem to have some bearing on the theory of the origin of platelets from the red cells, recently revived by Watson Without entering into this discussion, it seems worth while to record the observation that in only one of the cases in which we have observed an unusual amount of fragmentation was there a platelet count above the average

We have thought, too, that the appearance of these fragments is not consistent with some of the theories of red cell structure. All of the fragments large enough to study retain the typical hemoglobin color. As they are evidently pieces of cell membrane, the hemoglobin must be firmly attached to it. Pepper and Farley have advanced a similar argument.

<sup>\*</sup>Since the above was written we have had opportunity to see the blood of a patient with sickle cell anemia whose spleen was removed about two years ago. Her hemoglobin has remained close to 8 gm for some time. This blood is like that of crythroblastic anemia in having many budding forms and small fragments though the picture is not an extreme one. There is here also a high percentage of reticulocytes

We are presenting these studies in the hope that others may be in duced to make the moist film a part of their routine of blood investi gation, as we believe that valuable information regarding the pathogenesis of the anemias is to be gained in this way

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#### PEDIATRICS—WHAT IS IT!

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PEDIATRICS is not a specialty comparable to surgery, neurology, and orthopedies, but is instead general practice limited to the care of children from birth, or even before birth, to the age of fourteen years. In the care of children, the prevention of disease is more important than its diagnosis and treatment. There is a closer relationship between general practice and pediatrics than between the latter and the other specialties, because many physicians in general practice spend a large proportion of their time in pediatrics. Bass¹ recorded that over 20 per cent of the daily work of one hundred and fifty physicians in general practice was with children, and the experience of others has shown that as high as 60 per cent of family practice is in the age group below fifteen years. As Grulee² expressed it, pediatrics is separated from internal medicine by a horizontal line rather than a vertical one.

Pediatrics has five important overlapping functions, largely preventive, and most physicians are interested in them to different degrees (1) The care of the newly born, with recognition of jaundice, bleeding, malformations, etc., (2) feeding, and diet regulation, nutrition, periodic examinations, the training of infants and children in health habits, etc., (3) immunization against diphtheria, smallpox, etc., as well as the prophylaxis of scurvy, pellagra, rickets and tetany, (4) the recognition of ill children (this probably is one of the most neglected features of pediatrics), and (5) the diagnosis, prognosis and treatment of children's diseases, especially during their early and curable stages

Infant mortality in this country is higher than it should be. There are two alternative methods of reducing it, (a) the prevention of every condition possible, and the diagnosis and treatment of all other diseases, or (b) the focusing of attention and efforts on the most serious conditions. The first, though ideal, is impractical, for it is neither possible as physicians to be omniscient, nor as medical teachers to instil complete knowledge in medical students. In this day and time, medical students and physicians, because of the accumulation of scientific details, must learn less and less about more and more, and consequently are being forced further and further away from the goal of complete knowledge. However, it is possible to concentrate ma-

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jor efforts on the narrower field of serious conditions in which the greatest good can be accomplished so that, knowing the incidence of disease, the evaluation of symptoms, and a clinical study of the individual patient can be stressed

Unfortunately, there is no agreement in regard to the most serious conditions in children Osler' once said Know syphilis in all its manifestations and relations, and all other things clinical will be added unto you" A clinical knowledge of tuberculosis was held in equally high regard Today, however, the picture is changed, and from a teaching point of view, it probably is wiser to emphasize that Wassermann reactions and intradermal tuberculin tests are much more important than are the clinical symptoms of syphilis and tuber culosis in children A Wassermann test should be done on every child examined, regardless of chinical or social condition, and not only on those children suspected of having syphilis Certainly for every case of syphilis in children diagnosed by clinical signs, five are discovered by routine Wassermann tests An intradermal tuberculin test which is negative, with rare exceptions, will eliminate the possibility of tuberculosis, while if it is positive, the taking of the temperature night and morning usually will demonstrate, in most cases, whether the dis ease process is active or quiescent. Stewart has stated that in the discovering of childhood tuberculosis if a value of 100 per cent is assigned to the intradermal tuberculin test as a measure of its efficiency, the roentgen examination has a reliability of about 25 per cent, while a physical examination has an efficiency of a small fraction of 1 per cent Of course it is popular in 1933 to criticize such statements as the foregoing, on the basis that more time should be spent studying clinical symptoms and less reliance placed on laboratories However the methods which are scorned today as too scientific and nonclinical are likely to be the accepted clinical technics of future generations to wit the stethoscope, which now is regarded as the keystone of bedside medicine was ridiculed when Laennes introduced it in 1819 As late as 1840 Samuel Chew s pre ceptor protested that medical auscultation is wholly useless and I can investigate diseases of the cliest without that mode of examina tion better than any one else can with the help of a cartload of stethoscopes ''s

Nevertheless notwithstanding the complexity of the situation some progress toward a decision as to the most important pediatric conditions can be made by classifying these diseases in at least three ways (1) By determining their relative incidence from outpatient and hospital records (2) by discovering their relative severity through a study of mortality rates, and (3) by arranging them on the basis of those which are preventable by antenatal, natal, and postnatal meas-

ures, those amenable to specific therapy, and the remainder which, at present, cannot be prevented or cured

The relative frequency of children's diseases has been demonstrated by Arena and Harriss,<sup>6</sup> who found in 150,539 cases of 346 different

 $\begin{array}{c} \text{Table I} \\ \text{Relative Frequency of Diseases Among 80,000 Outpatient and Hospital} \\ \text{Children}^6 \end{array}$ 

FREQUENCY

(CASES OF EACH DISEASE)	ENT DISEASES
Over 200 (seen at least once per month)	86 (25%)
101 to 200 (seen every other month)	23 (7%)
26 to 100 (seen twice per year)	65 (18%)
5 to 25 (seen once per year)	89 (26%)
0 to 4 (seen every five years)	83 (24%)
Total cases 150,539	346 (100%)

NUMBER OF DIFFER

TABLE II

FIVE PRINCIPAL CAUSES OF DEATH IN EACH AGE GROUP (U S REGISTRATION STATES, 1926)<sup>7</sup>

$_{ m AGES}  ightarrow$	UNDER 1 YR	1 YR.	2 YR.	3 YR.	4 YR.	5 TO 9 YR.	10 TO 14 YR.
Total deaths, all causes	159,411	31,609	14,144	9153	7018	22,779	17,263
CAUSE	]	PERCENTA	GE OF DE	ATHS IN	EACH A	GE GROUP	
I. Intestinal diseases							
(Diarrhea and		Ì		-		1	
enteritis)	13	20	11	7		i	8
II Chest diseases							
(Pneumonia and in	ļ						
fluenza)	18	32	27	21	17	13	11
III Heart disease						в	10
IV Accidents		6	11	16	19	22	21
V Infectious diseases		]					
Whooping cough	3	8 8	;				
Measles		8	8	6	5		
Diphtheria	1	1	8	11	12	9	
Tuberculosis	1	İ			5	6	10
VI Miscellaneous							
Malformations and	İ						
causes associat	}	Ì					
ed with early	1	1					
infancy	46						
Ill defined group	4						
Summary of percentage							
of deaths due to five	]	}	]				
principal causes in		1					
each age group	84	74	65	61	58	56	60

diseases among 80,000 children admitted to the outpatient department and wards of a large children's hospital over a period of twenty years, that eighty-six diseases were common enough to occur at least once per month, and that twenty-three additional diseases were seen on an average of every other month, and that the remaining two hundred and thirty-seven occurred less than twice per year (Table I)

However, it is difficult to be constantly on the alert for even eighty six diseases, not to mention three hundred and forty six

The second method of classification of pediatric disease is based upon the death rate, and directs its emphasis upon the number of deaths which each condition causes, as shown in Table II. The first or intestinal group consists largely of diarrhea and dysentery (enteritis), which, fortunately, are readily diagnosed and usually adequately treated. However, practically all of these cases could have been prevented if the infants had been fed whole lactic acid milk and had been kept in sanitary and fly free surroundings. In the second or chest group empyema probably is the most important cause of death because at autopsy, pus can be found in the pleural cavities of a large percentage of children who have had pneumona. Early diagnosis of this complication and its adequate surgical treatment might have prevented many of these deaths. Repeated needling and fluoroscopic and x ray examinations are essential in the search for empyema after

TABLE III

PRINCIPAL CAUSES OF DEATH IN A LARGE CHILDREN'S HOSPITAL<sup>3</sup>

CAUSE OF DEATH	NUMBER OF DEATHS
I Intestinal disease	
(Chiefly dysentery and diarrhea)	53 (23%)
II. Cliest diseases	,,
(Pneumonia and empyema)	44 (20%)
III. Heart disease	44 ( 20%) 10 ( 4%)
IV Neurological diseases	1 -707
(Chiefly meningitis)	52 ( 22%)
(Chiefly meningitis)  V Miscellaneous	52 ( 22%) 70 ( 81%)
Total	2-9 (100%)

pneumonia The third group of heart disease is more important from the prognostic point of view than from the therapeutic. One occasion ally hears of physicians who cure heart disease but up to the present, alleviation of symptoms and attempts to prevent further damage are the best that can be done. The fourth group of accidents is increasing rapidly in importance because of automobiles. Every child must be instructed in caution. The fifth or infectious disease group should not occur at all, for these diseases are preventable. As can be seen from the summary of Table II those five groups account for 34 to 74 per cent of the deaths in each age group of children.

Arrangement of the 229 deaths for the year 1931 at the Harriet Lane Home (Table III) presents a slightly different picture of the most dangerous diseases. Three of the five groups mentioned above are the same namely intestinal chest and heart diseases but deaths from infectious diseases and accidents do not appear because they were reported among patients admitted to other departments. The most interesting difference shown by Table III is in the number of deaths from meningitis. The explanation probably is twofold, first,

because many very ill patients suffering from this disease are sent to the Harriet Lane Home, and second, because in statistics gathered from the whole country (Table II), a number of deaths really resulting from meningitis are not recognized, nor reported as such Meningococcus meningitis, a curable disease, forms one-fifth of group IV

Table IV

Comparison of the Causes of Death from All Causes by Age in Children under

Fifteen Years\*

	UNDER FIF-	I		
	TEEN YEARS	UNDER FIVE	FIVE TO	TEN TO FIF-
AGE	(PER	YEARS	NINE YEARS	TEEN YEARS
	CENTAGE OF	(PER	(PER	(PER
	TOTAL	CENTAGE)	CENTAGE)	CENTAGE)
	DEATHS)			
I Epidemic and infectious diseases including tu berculosis	19	17	33	28
(Tuberculosis from all causes, included in I)	(3)	(2) (1% under 1 yr)	(5)	(10)
II General diseases not in cluded in I	3	$\overline{2}$	5	7
III. Diseases of nervous system and special sense organs	3	3	6	6
IV Diseases of circulatory system	2	1	6	11
V Diseases of the respiratory system	14	15	9	7
VI Diseases of the digestive system	15	16	13	13
VII. Nonvenereal diseases of the genitourinary sys tem	1	1	2	3
XI Malformations	6	7	1	1
XII. Early infancy	25	29		
XIV External causes, acci dents, etc	7	4	23	22
XV Ill defined causes, and IX Diseases of the skin, and X, Bones (IX and X were each less than 0 25%, VIII, Puerperal state, and XIII, Old age, do not fall in these age groups)	4	5	2	2
Total	240,661	199,507	23,389	17,765
	(100%)	(100%)	(100%)	(100%)
Percentage of total by age	100	84 (61% in 1st yr)	9	7

<sup>\*</sup>Deaths (exclusive of stillbirths) from each cause by age in the registration area and each registration state 1927 Mortality Statistics 1927 Part I Tables and General Tables Bureau of the Census U S Department of Commerce U S Government Printing Office, 1929 (Note All of the deaths from bacillary dysentery and enteritis are counted as dysentery because experience has demonstrated that dysentery bacilli are responsible for the majority of these deaths. Half of the deaths from bronchopneumonia, lobar pneumonia, and pneumonia, unspecified have been counted as empyema for at autopsy many of the children have empyema which usually has not been recognized. All of the deaths from rheumatic fever chorea, pericarditis endocarditis and myocarditis have been grouped as practically all of them are due to infection with the so-called rheumatic virus)

in Table III The fifth or miscellaneous group contains deaths from syphilis and prematurity which might not have occurred, had ante natal and postnatal treatment of the mother and child by the attending physician been adequate

Table IV, based on the mortality statistics of 1927, confirms the facts recorded in Tables II and III, and also emphasizes the need of more and better preventive pediatries, because it demonstrates that five groups of diseases and conditions are responsible for 80 per cent of all the deaths in children under fifteen years of age, namely, I-epidemic diseases (19%) V-respiratory diseases (14%), VI-di gestive diseases (15%), XII-diseases of early infancy (25%), and XIV-external causes (7%) Most of the diseases and conditions in these five groups are curable if recognized early, and many of them are preventable. The most emphasis should be placed on the prevention, recognition and treatment of the diseases and conditions which occur in pre-school children, and especially should antenatal and natal care be stressed, because 61 per cent of the deaths in chil dren occur during the first year of life, and most of them are in early infancy The need for precautions against tuberculous infection and for its early diagnosis and adequate care also is demonstrated by Table IV because deaths from tuberculosis increase in the older age groups, from 1 per cent of the deaths under one year to 2 per cent of those under five years, 5 per cent of those from five to nine years and to 10 per cent of those from ten to fourteen years. However the picture is not altogether true for the great number of deaths from all causes in early infancy produces a misleadingly low percentage of deaths from tuberculosis

According to the third method of classification the diseases among children can be arranged in five subgroups (A) those preventable by antenatal and natal measures (birth injuries conditions of early infancy, gonorrheal ophthalmia premature and stillbirths and syphi lis), (B) those preventable by postnatal measures (accidents, ane mia, dietary deficiencies (pellagra rickets scurvy, and tetany) diph theria, dysentery (bacillary), malaria malnutrition, measles, pertus sis, poisoning rabies, scarlet fever smallpox tetanus tuberculosis, and typhoid paratyphoid fever) and (C) conditions amenable to specific therapy (abscesses, allergy bronchitis convulsions, diabetes, di etary deficiencies diphtheria epilepsy crysipelas, fungus infections lung abscess malaria, meningitis, otitis media, parasites (intestinal) syphilis thymus enlargement and tuberculosis) To this last groun should be added such surgical conditions as appendicatis, empyema intestinal obstruction intussusception mastoiditis, and pyloric steno Every physician and pediatrician should be on guard constantly that these conditions are not overlooked. The last two subgroups are (D) all other epidemic and infectious diseases, some of which can be

TABLE V

COMPARISON OF THE PREVENTABLE, CURABLE AND NONPREVENTABLE DEATHS BY AGE, IN CHILDREN UNDER FIFTEEN YEARS	UNDER 1 YR. 2 YR. 3 YR. 4 YR 0 NDER 5 TO 9 10 TO 14 1 YR. (PER CENT) (PER CENT) (PER CENT) (PER CENT) (PER CENT) (PER CENT)	42 1 1 1 31 1	18 46 42 42 42 25 37 39	9 14 14 13 13 10 17 20	3 6 6 6 6 5			72 67 63 62 70 61 55	28 33 37 38 30 39 45 45	
, пу Спп	R. 4 ENT) (PEI						*****			! 
ву Абе,	3 YI	1	42	13	9			62	38	8,82
в Dеатив	2 YR. (PER CENT	1	42	14	9			63	37	12,256 $(100%)$
PREVENTABL	1 YR. (PER CENT)	H	46	14	9			- 67	33	24,405 (100%)
E IND NON	UNDER 1 YR. (PER GENT)	42	18	6	ဆ			72	58	147,134 (100%)
вьк, сивлы	UNDER 15 YR. (PKR CENT)	56	27	21	3			77	23	240,661 (100%)
COMPARISON OF THE PREVENTAL	AGE →	A Antonatal and natal preventable causes	B Postnatal preventable causes	C Causes curable by specific therapy	D All other epidemic and infectious	causes, some of which can be	santary measures	Total proventable and curable diseases and conditions	E All other discases which at pres ont cannot be prevented or cured by specific measures	All diseases and conditions

eliminated by public health and sanitary measures (mumps, influenza, poliomyelitis, etc.) and (E) all other diseases and conditions most of which, at present cannot be prevented or cured by specific therapy (encephalitis leukemia malformations etc.)

This third type of classification is an ideal one because it stresses the preventive aspect of pediatries, a phase which cannot be too strongly emphasized because as shown in Table V 77 per cent of all the deaths among children in 1927 were due to diseases and conditions which might have been prevented or cured. One quarter of the conditions which kill 240,661 children annually (Table V) can be prevented by antenatal and natal measures one quarter by postnatal means, and one fifth can be cured by specific therapy. An example of what can be done by antenatal care is Gengenbach 8° report that the infant mortality was 178 per 1 000 live births from mothers who did not make antepartum visits to their physicians, and only fifteen from those who made nine or more visits. An encouraging study of the benefit of postnatal measures is that of Brooks<sup>10</sup> who recorded that the infant mortality among the colored infants of a Southern city fell

TABLE VI

COMPARISON OF THE PREVENTABLE, CUBABLE AND NONPREVENTABLE CAUSES OF DEATH
IN A LARGE CHILDREN'S HOSPITALS

CAUSES OF DEATH	NUMBER OF DEATHS
A. Antenatal and natal preventable causes	38 (17%)
B. Postnatal preventable causes	84 (36%)
O Curablo causes	20 (11%)
Total preventable and entable discases	148 ( 64%)
E Nonpreventable diseases	81 ( 36%)
All diseases and conditions	229 (100%)

from 196 to 119, and that of the white infants from 83 to 57 during the four years in which the visits to the well baby clinics rose from zero to 3,380

The facts emphasizing the need of preventive measures and early diagnosis and adequate treatment of pediatric conditions can be seen perhaps more clearly by studying an analysis (Table VI) of the 229 deaths which occurred among the 1052 children admitted to the Harriet Lane Home. Over 50 per cent of these deaths could have been prevented if prophylactic measures had been used by the family pediatrician or general practitioner, and part of an additional 11 per cent might have been averted if a diagnosis had been made earlier and the children sent to the hospital before specific therapy was too late. The figures in Table VII, compiled from one thousand autopsies, are not so striking, but they do demonstrate that nearly half of these deaths were from preventable and from curable causes.

The need for focussing attention on the diseases which can be prevented or cured by specific therapy is shown in Table VIII, compiled

from the figures of Arena and Harris <sup>6</sup> Eighty-two per cent of the 150,539 cases might have been prevented, or the patients cured, while only 62 per cent of the three hundred and forty-six diseases themselves are preventable or curable. In other words, as shown in Table IX,

TABLE VII

THE CAUSES OF DEATH IN 1,000 CONSECUTIVE AUTOPSIES IN CHILDREN UNDER FOUR
TEEN YEARS OF AGE!1

CAUSES	NUMBER
A Antenatal and Natal Preventable Causes	
Syphilis	20
Prematurity	23
Cerebral hemorrhage	12
A Subtotal	55 (5%)
B Postnatal Preventable Causes	
Tuberculosis	96
Gastroenteritis	25
Dysentery	8
Intorication	70
Marasmus	37
Contagious diseases	47
Accidents	8
B Subtotal	291 (29%)
C Causes Curable by Specific Therapy	
Empyema	20
Meningitis, purulent	64
Mastoiditis	30
Surgery	10
Intussusception	iĭ
C Subtotal	135 (13%)
Subtotal of Preventable and Curable Causes	481 (48%)
E Causes Not Preventable, or Curable by	<del></del>
Specific Therapy	
Pneumonia	157
Septicemia	83
Congenital malformation	90
Heart disease (acquired)	42
Atelectasis	8
Status lymphaticus	15
Neoplasms	17
Peritonitis	33
Nephritis	15
Encephalitis	7
Diseases of the blood	11
Miscellaneous	25
Undetermined	26
E Subtotal	519 (52%)
Total	1,000 (100%)

the incidence of cases is higher in the preventable and curable group For example, among 43 per cent of the preventable and curable discases, the frequency was over one hundred cases per disease, while only 13 per cent of the diseases which cannot be prevented or cured by specific measures had this high incidence

In order that one may arrive at a decision as to the most important disease, they have been arranged in Table X from all three stand-

points (1) Relative incidence, (2) relative mortality, and (3) preventability or curability. Fortunately there is no correlation between the frequency and the mortality of disease for example, abscesses are the most common condition in children, but they are only forty fourth in relative mortality. As a general rule, the diseases in children for which medical and is most frequently sought, do not endanger life. However it is rather humiliating to us in the medical profession that the diseases which cause three-quarters of the deaths in children

TABLE VIII

A COMPARISON OF THE NUMBER OF CASES AND THE NUMBER OF DISEASES AMONG OTHER CONDITIONS AMONG 80 000 OUTPATIENT AND HOSPITAL CHILDRENG

CAUSES	NUMBER OF CASES	NUMBER OF DISEASES
A Antenatal and natal prevent able causes	3,550 ( 2%)	9 ( 8%)
B Postnatal preventable causes	44,626 ( 80%)	33 ( 9%)
C Causes curable by specific ther apy	72,007 (40%)	163 (47%)
D Causes preventable by public health measures	1,216 ( 1%)	n ( 3%)
E. All other causes most of which are not preventable, or	20150 (104)	
curable by specific thorapy	28 150 ( 18%)	132 ( 38%)
Total	150 539 (100%)	346 (100%)

TABLE IX

COMPARISON OF THE FREQUENCY OF PREVENTABLE AND CURABLE DIRECTED AND OTHER CONDITIONS AMONG 80 000 OUTPATIENT AND HOSPITAL CHILDRENS

INCIDENCE (CARDS OF EACH	ARLE A	ND	PREVENT CURABLE SES			
Over 200		73	7	84%)	13	(10%)
101 to 200		19	Ć	9%)	4	( 8%)
26 to 100		47	7	22%)	18	(18%)
5 to 25		43	~	20%)	46	(85%)
0 to 4		82	(	15%)	51	(30%)
Total cases	150,539	214	(1	.00%)	132	(100%)

can be prevented, or cured by specific therapy. The most important diseases, therefore, are those which can be prevented or cured, and the greatest emphasis should be concentrated on recognizing them and on teaching medical students to become familiar with them. Pediatrics can be of the greatest service to the public if in its practice emphasis is placed on the prevention of disease and upon periodic examinations of children for the early detection of disease or disease tendencies, rather than using it as consultative service. For example, it has been found by the investigators of the White House Conference and by others that the health of children who are brought at regular intervals to a physician's office is better than that of those who have medical care only during acute illnesses. Also it is true that for every

TABLE X

THE ONE HUNDRED MOST IMPORTANT DISEASES AND CONDITIONS IN CHILDREN

_										
A	Antenatal	and	Natal	Preventable	Causes	(Responsible	for	One quarter	of	the
				Deaths A	Imong (	Children)		=	•	

CONDITION	RELATIVE IN OIDENCE*	RELATIVE MORTALITY
Birth injuries	44x	6
Conditions of early infancy (atelectasis, suffocation, debility, icterus, sele		
rema, etc.)	94x	5
Gonorrheal ophthalmia	83	57
Prematurity	36	1
Stillbirths	99x	95
Syphilis	23	18
Subtotal A (6 conditions)	2%	26%

### B Postnatal Preventable Causes (Responsible for One quarter of the Deaths Among Children)

Accidents (incl trauma)	66x	13
Anemia	31	45
Chickenpox	46x	68
Dehydration	93x	71
Dietary deficiencies (pellagra, rickets,		
scurvy, carious teeth, tetany)	2	87
Diphtheria	33x	7
Dysentery (bacıllary)	25	3
Enuresis	29	74
Feeding regulation	4	75
Intertrigo	56	81
Malaria	89	29
Malnutrition	13	83
Measles	35 <b>x</b>	15
Nutritional disturbances	7	4
Pertussis	17 <b>x</b>	9
Poisoning	63	64
Rabies	100x	58
Scarlet fever	51 <b>x</b>	19
Smallpox	98	60
Tetanus	96	33
Tuberculosis (incl. the meningitis)	9	10
Typhoid paratyphoid fever (typhoid,		
para A, para B, B suspestifer)	59	27
Vaginitis	34	100
· ·	_	
Subtotal B (23 conditions)	30%	27%

## C Causes Curable by Specific Therapy (Responsible for One fifth of the Deaths Among Children)

Abscesses	1 1	44
Acidosis	80x	66
Adenoids	14	65
Allergy (exc urticaria)	12	51
Anemia (see B)		
Appendicitis	85x	16
Arthritis	37	<b>54</b>
Bacteremia	64	47
Behavior problems	16	67
Bronchitis	11	17
Chorea	38	61
Conjunctivitis (exc gonococcus)	28	69
Constipation	39	70
Convulsions	67	24
-Dehydration (see B)	1	
Dermatitis	41	72

TABLE X-CONT'D

C Causes Curable by Specific Therapy (Responsible for One-fifth of the Deaths
Among Children)

CONDITION	RELATIVE	RELATIVE
	INCIDENCE	HORTALITY
Diabetes mellitus	00	89
-Deficiency diseases (see B)		I
-Diphtheria (see B)	1	1
Dysontery (ameble)	97	73
Empyema	58	88
Epilepsy	43	43
Erysipelas	72	31
Eye abnormalities	26	59
Fracture	61	76
Fungus infections	55	53
Gastritis	09	41
Hemophilia	95	77
Hemorrhagic disease of the newly born	88	78
Hernia	15	49
Hydrocelo	70	79
Impetigo	21	80
Intussusception and intestinal obstruction	8,	22
Laryngitis	52	46
Lung abseess and bronchiectasis	92	63
-Malaria (see B)	,-	1
Mastoiditis	75	35
Meningitis (mge)	68	80
Millarin	78	84
Neurosis	40	85
Otitis media	3	28
Parantes (intestinal)	45	52
Pedienlosis	50	86
Pneumonia	8	2
Prepuce abnormalities	19	87
Purpura	86	88
Pyloric stenosis	79	89
Pyuria	82	62
Retardation (physical)	78	91
Rheumatic fever	47	32
Scables	80	93
Sinneitie	82	94
Stomatitia	27	48
-Syphilia (see A)	1 21	10
Tie	74	96
Tonsils hypertrophy of	10	97
Thymus enlargement	84	26
Thyroid abnormality	81	56
Ulcers	77	98
-Tuberculosis (see B)	1 "	""
Tumors (abdom, brain misc.)	42	34
Urticaria	54	99
0.100.10	1 03	1 ==
Subtotal C (55 conditions)	45%	21%

TABLE X-CONT'D

E Common Diseases Which at Present Cannot Be Prevented or Cured by Specific Measures

CONDITION	RELATIVE INCIDENCE*	RELATIVE MORTALITY
Encephalitis	60	36
Heart disease (acquired)	24	12
Heart disease (congenital)	48	8
Hydrocephalus	71	25
Jaundice	53	82
Leucemia (all types)	91	42
Lymph node enlargement	20	50
Malformations	22	14
Nephritis	57	21
Peritonitis	76	40
Retardation (mental) (incl idiocy)	18	90
Rhinopharyngitis	5	92
Tonsillitis	6	20
	l —	
Subtotal E (13 conditions)	17%	10%
	<u> </u>	<b>—</b>
Total $A + B + C + D + E$ (100 conditions)	95%	87 <i>%</i>
246 remaining diseases and conditions	5%	13%
Total 346 diseases and conditions	100%	100%

<sup>\*</sup>Based upon 150 539 cases of 346 diseases and conditions among 80 000 children in the Harriet Lane Home, Johns Hopkins Hospital 1912 to 1932 figures marked (x) are not representative of the true relative incidence, because patients suffering from these conditions usually were on other services 1e conditions of early infancy and stillbirths on the obstetrical service accidents and appendicitis on the surgical service, diphtheria, measles and scarlet fever on the contagious service, etc. 1 indicates the most common disease 100 the least. (Arena, J. M. and Harriss R. Census of the diagnosis file of the Harriet Lane Home [in press])

†Based upon 240 661 deaths among children under fifteen years of age 1927 USA. Wortality Statistics 1 indicates the highest number of deaths 65 the smallest no figures could be obtained for those conditions marked 66-100

dollar paid by the paients of children who are brought regularly to their physicians' offices, three dollars are paid by those who call for medical aid only during emergencies

#### SUMMARY

As may be seen in Table X, if proper antenatal, natal and post natal preventive measures are perfectly performed, the twenty-nine diseases in groups A and B can be reduced to a minimum, and the pediatrician or family physician can confine his efforts to the diagnosis and treatment of the fifty-five conditions amenable to specific therapy. In other words, instead of trying to teach students and ourselves to recognize three hundred and forty-six diseases, the prevention of twenty-nine, and the treatment of fifty-five should be stressed. These preventable and curable diseases cause 77 per cent of the deaths in children. The present reduction of general mortality largely has been due to efforts to prevent disease, and future progress probably will consist in improving the medical and hospital care of patients, but in pediatrics, as these figures only too clearly demonstrate, emphasis on both phases must be increased. If a physician is trained to recognize ill children, if he will carry out the immunization measures which are

recommended by the White House Conference, and if he will feed clul dren simply and sensibly, the practice of pediatries will progress, the public will be benefited, and infant mortality decreased. If the doc tors, health departments and public will cooperate, this goal can be reached. Much of the present situation is due to the apathy and in difference of the public, and not to any unwillingness of the medical The accusation of Lady Mary Montagu is as unfounded today as it was in 1717 "I am patriot enough to take pains to bring this useful invention (smallpox inoculation) into fashion in England, and I should not fail to write to some of our doctors very particularly about it, if I knew any one of them that I thought had virtue enough to destroy such a considerable branch of their revenue for the good of mankind But that distemper (smallpox) is too beneficial to them. not to expose to all their resentment, the hardy wight that should undertake to put an end to it Perhaps, if I live to return, I may, however, have courage to war with them Upon this occasion, admire the heroism in the heart of-vour friend Mary Wortley Montagu 'n

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## SERUM PROTEINS AND LIPOIDS IN THE ECZEMA OF INFANTS AND CHILDREN

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IT IS now some twenty-eight years since Czeiny¹ introduced the term "exudative diathesis" into medical nomenclature. His purpose was in part to remove the confusion with tuberculosis which the older term "scrofula" (Skrophulose) involved, but mainly to emphasize his conception of the disorder as one based on heredity and constitution in which metabolism, particularly of the fats, was seriously at fault and of which the skin disturbance was but one manifestation. Although at that time the modern conception of allergy had not been defined and elaborated, Czerny called attention to the importance in the clinical picture of idiosyncrasies to various foods, to the frequency of urticaria, and to the occurrence of asthma and allied respiratory disorders as a later event in patients with the evudative diathesis. While today, at least in America, the term is not widely used, it has played an important part in developing the now generally accepted view that what is usually called "infantile eczema" is in reality but one of the evidences of a constitutional anomaly

In many respects our knowledge of the basic nature of this common and distressing disorder remains defective. An enormous literature has grown up around the subject, which it is impossible to review in this paper (see the recent publications of Moro<sup>2</sup> and Hill<sup>3</sup>). That a state of allergy occurs in a large proportion of cases is well established but whether this is the primary or a secondary phenomenon is uncertain. The recent study of Smyth, Bain and Stallings<sup>4</sup> would appear to indicate that skin allergy, at least is characteristically a later development, increasing notably from the earlier to the later months of the first year, and that hypersensitiveness of the skin to various nonspecific irritations definitely precedes it

In the search for clues to the nature of the underlying disturbance rather than with preconceived notions as to what this might be, we have made some analyses of the blood of a sort previously little studied. These included the total protein, the albumin, the globulin, the cholesterol and (in part of the cases) the lipoid phosphorus

Previous studies of the serum proteins and lipoids in the eczema of infants and children are few and present observations in small num bers of cases only. Ribadeau Dumas and Levy, using the Kjeldahl method, reported a slight hypoproteinemia in 5 infants with active eczema, and normal figures in 3 others after healing. Goldbloom and Gottheb reported high cholesterol in 3 of 4 cases of cezema, they used whole blood, not serum, and their absolute figures are not comparable with ours. In other reports found in the literature the patients were either adult, or the age was not stated. The study of Perutz and Klein on adults may be mentioned, since they found high albumin/globulin ratios and high osmotic pressures in the serum during the stage of repair in eczema while the values were approximately normal during the acute stages.

#### METHODS

Total protein was determined by the gravimetric method of Barnett, Jones and Cohn \* The same method was also used for albumin after separation of this protein fraction with half saturated ammonium sulphate. Globulin was also similarly determined but the figures used in the present report represent determinations by difference (total protein-albumin), since the amounts of globulin in most of the samples were too small for entirely satisfactory accuracy in direct measurement. The method of gravimetric measurement has an important advantage over other methods available for the analysis of small samples of blood, being more accurate in our opinion than micro-Kjeldahl measurements, and quite independent of possible variations in amino acid composition of the proteins, as contrasted with colorimetric methods.

Cholesterol was determined by the method of Myors and Wardell. The lipoid phosphorus was determined by a combination of the methods slightly modified, of Bloorie (preliminary extraction) and Benedict and Thelati (determination of phosphorus)

Colloid osmotic (one otie) pressure was estimated by the formula of Gorvaerts. 20 Osmotic pressure  $\Longrightarrow$  (albumin  $\times$  5.5) + (globulin  $\times$  1.4) The accuracy of this formula in correspondence with the actual one otic pressure of the serum as a whole is perhaps not entirely satisfactory but probably gives a reasonable approximation.

#### MATERIAL

Fifty infants and children with typical eczema were studied. Total protein was determined in all of these albumin (and, hence, the derived figures for globulin albumin/globulin ratio osmotic pressure) in 46 of them. For comparison samples of blood were taken from 36 infants and children without eczema present or past and either in good health or brought to the clinic for minor complaints. In one of these the distribution of albumin and globulin was manifestly abnormal (albumin, 159 globulin 519) and in one the cholesterol (297 mg per cent) was extremely high both these were excluded from the computations of the control figures

Our serum samples being small cholesterol and lipoid phosphorus were determined in the alcohol-ether washings of the protein precipitates.

T'ABLE I

	LOTAL	TOTAL PROT	ALBUMIN	MIN	GLOBI	GLOBULIN			ONC	ONCOTIC	CHOLESTEROL	STEROL	Ξ	ID P
	8	GM	GM		MD		A/G R VTIO	OLLA	PRESSURE	SURE	MG	¢	ЭЖ	0
	PER	PER CENT	PER CENT	ENT	PER C	ENT			MM IIG	ПС	PER (	PER CENT	PER CENT	ENT
	CNTR	EOZ	CNTR	ECZ	CNTR	NTR ECT	ONTER	ECZ	ONTR	ECZ	CNTR	ECZ	CNTR	ECZ
No cuses	36	20	35*	,	37	9#		40	35* 46	46	33*	33* 42	21	22
Menn	6 73	089	4 75		2 01	183		3 03	28 44	30 27	163 7	2003	8 76	8 58
Median	0.20	6 93	4 81		1 93	177		2 70	28 80	30 55	1702	200 0	$^{7}76$	8 43
Prob error (±)	0 20	0.51	0 35	0.45	0 48	0 37	0.56	0 67	180	2 37	17 0	31 5	2 05	1 06
Diff means (per cent contr mean)		+5%				%G-		+12%		+5%		+22%		%i-
Per cent eases over contr mean	20%	28%	21%		43%	33%	27%	29%	%09	20%	55%	81%	30%	41%
*One case omitted														

Cholesterol was determined in 42 of the eczema group, and 34 of the control group Lipoid phosphorus was determined in 22 of the former, and 21 of the latter

The age distributions of the two groups were reasonably similar In the eezema group, 12 (24 per cent) were six months or less, 14 (28 per cent) between six months and a year, 12 (24 per cent) between one and two years and 11 (22 per cent) two years or older in one case the age was not stated. In the control group, 9 (25 per cent) were six months or less, 7 (19 per cent) between six months and a year, 6 (17 per cent) between one and two years, and 14 (39 per cent) two years or older. Since the main physiologic changes in proteins and lipoids occur during the first six months and the main differences between the age distributions of two groups occurred after the age of six months, we believe that the latter are not of significant proportions for our purposes

#### EXPERIMENTAL RESULTS

Total Protein—No significant difference in total protein is detectible between the groups with and without eczema. The former show a slightly higher average figure, and about 8 per cent more of the eczema sera than of the controls were above the normal average. The variability is equal in the two groups

Serum Albumin—The difference between the two groups is some what more striking than is the case with total protein, but not, per haps sufficient to constitute statistical significance. The eczema aver age is 7 per cent higher than that of the controls, and 10 per cent of the cases showed figures greater than the control average. The variability in the former was however greater than in the controls. On the whole a tendency to higher scrum albumin in eczema is suggested by the data, but it is manifestly inconstant.

Serum Globulin —As might have been expected from the total protein and albumin, the globulin percentages in the eczema group are, on the average, somewhat lower (9 per cent) than in the control group Sixty seven per cent of the eczema group showed figures for globulin lower than the control average. The variability is distinctly lower in the eczema than in the control group

Albumin/Globulin Ratios —The mean of the eczema group is 12 per cent higher than that of the control group, but the variability is quite large. Some extreme deviations of the ratios occurred in the eczema group, in four instances, they were in excess of 45 and in one instance, reached the remarkable figure of 77.

Osmotic Pressure of the Proteins (Oncotic Pressure) —The tendency to slightly higher total protein and considerably higher albumin fractions in the eczema group indicated that the protein osmotic pressure yould be abnormally high in many cases—This was found true, since

T'IBLE I

	1 TOTAL	TOTAL PROT	ALBUMUN	MIN	GLOBI	TLIN			ONCOTIO	CHOLESTEROL	TEROL	LIPO	100
	6				N D		A/G R \TIO		PRESE	MG		MG	m
	PER	CENT	Ā	ENT	PER C	ENT			11.11	PER C	ENT	PER CENT	ENT
	CNTH	NTR   FCZ	CNTR		CNTR	CNTR ECZ	ONTR	ECZ	CNTR   ECZ	CNTR ECZ	ECZ	CNTR	E
No sugar	98	2.0			35*	107	35		35*	33*	42	21	22
Most	6.73	0.80			0.0	1.83	2 60		28 44	163 7 2	300	8 76	8 58
Media	0.20	0 0 0			1 93	1 77	20 2		28 80	170 2 2	0 00	7 76	8 43
Deal case (4)	010				870	0.37	0.56		1.86	17 6	31.5	2 05	106
True Grief (2)	) 	100			}	206-					.22%		<u>-2%</u>
Por cent cases over contr mean	20%	58%	61%	61%	43%	33%	24%		200	55%	81%	39%	41%

however, not accurately quantitative and was also positive in some of our controls We are, therefore, unable to draw any direct con clusions from our few precipitin tests

The hypercholesteremia occurring in at least half of our cases of eezema-the most constant abnormality noted-as well as the much greater "scatter" of the figures for cholesterol in that group (one of which was as low as 70 mg per cent), while of obscure significance, suggest a marked instability of cholesterol metabolism as a frequent, though not constant, accompaniment of eczema

#### CONCLUSIONS

- 1 In the eczema of infants and children, apparently independent of age or the state or stage of the disease, the composition of the serum protein frequently but not constantly shows deviations from the normal. The commonest changes in the proteins are high al bumin, low globulin, and a high albumin/clobulin ratio all of which occur more frequently in patients with eczema than in those without These changes involve an increase in the calculated oncotic pressure of the serum. It is to be emphasized that the changes when observed are not except in a minority of cases extreme, they are not constant or suggestive of more than a secondary effect of the disease
- 2 An inconstant but much more frequent change is hypercholes In one half of the cases of eczema the level of serum cholesterol was found to be in excess of 200 mg per 100 cc, and the average of the group as a whole was also slightly over that figure In a few cases the cholesterol was very low. The results indicate a certain instability in cholesterol metabolism in eczema, the signifi cance of which is not clear but which is probably to be regarded as a secondary or subsidiary manifestation of the general disturbance No differences in the phospholipids of the serum were detected in the eczema group as compared with the controls

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#### INTRACELLULAR FLUID LOSS IN DIARRHEAL DISEASE

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#### INTRODUCTION

THE process of the dehy dration of infants in the course of diarrheal disease may be briefly described Vomiting and diarrhea produce a loss of gastiointestinal secretions and thereby cause a withdrawal from the blood plasma of the water and materials used in the construction of these secretions The blood plasma is, however, sustained over a considerable interval, both as regards volume and composition, at the expense of interstitial fluid and the extensive loss of interstitial fluid which is so conspicuously evident in dehydrated patients is thus Eventually the interstitial reservoir is depleted and then, with dangerous rapidity, the volume of the plasma falls and distortions of the electrolyte structure of the plasma develop 1 It is thus apparent that an essential step in the repair of dehydration should consist in refilling the interstitial body fluid compartments usually accomplished by the subcutaneous administration of physiologic salt solution which provides the two quantitatively important electrolytes, sodium and chloride ion With more finesse, a solution which copies in detail the composition of interstitial fluid may be used 2

There remains for consideration the possibility that dehydration produces also a withdrawal of appreciable quantities of intracellular fluid. The implications of such an event must be considered in terms of the electrolyte content of intracellular fluid as compared with that of the extracellular fluids. As may be seen in the diagrams in Fig. 1, there are only slight differences in the relative values of the inorganic factors in the composition of blood plasma and of interstitial fluid. These differences are referable, in terms of the Donnan law, to the presence of the nonpermeating protein ions in the plasma. Intracellular fluid, however, presents an electrolyte pattern which differs widely from that of the extracellular fluids. Here, instead of sodium, potassium is the chief factor in the total fixed base value and phosphate almost replaces chloride. The mechanism which permits these large differences in the values for the individual electrolytes in the two adjacent fluids has not been discovered. It is evident from their

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chemical anatomy as described by the diagrams that intracellular fluid cannot be used, as is interstitial fluid, in support of the blood plasma and also that the materials therapeutically supplied for replacement of interstitial fluid will not repair a loss of intracellular fluid

Does the withdrawal of interstitial fluid which dehydration produces proceed without disturbance of intracellular fluid volume? There is evidence which indicates an accompanying loss of intracellular fluid. It has been found that when interstitial fluid is removed by

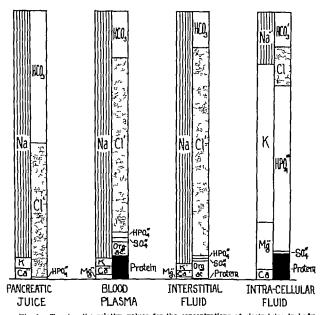


Fig 1.—Showing the relative values for the concentrations of electrolytes in body fluids. The values for the cations or potential base are superimposed in the left hand columns and those for the ackl radicles in the right hand columns. The data representing interstitial fluid are from cerebrospinal fluid and those for intracellular fluid are from muscle tissue.

diuretic agents there occurs also a much smaller but appreciable with drawal of intracellular fluid. Apparently, a reduction of the volume of interstitial fluid in the body does to some extent interfere with the maintenance of a normal volume in the adjacent intracellular compartment.

In the studies just cited the information regarding the source of the fluid removed from the body was obtained by measuring the excretion

of sodium and of potassium in the urine. If the fairly satisfactorily established proposition that a loss of electrolyte from the body is accompanied by a corresponding amount of water be accepted, measure ments of a loss of sodium and of potassium can, as the data in Fig. 1 indicate, be used to calculate respectively a withdrawal of extracellular and of intracellular water. This premise is used in an investigation of body fluid losses by infants in the advanced and severe stage of diarrheal disease, the results of which are presented in this paper. The chief item of attempt was to learn whether or not there is a considerable loss of intracellular fluid in addition to the large loss of interstitial fluid.

#### PLAN OF STUDY

Two infants were studied over a period of twenty-four hours im mediately following their entrance to the hospital Both were suffer ing severely from diarrheal disease with vomiting and were extensively dehydrated So far as could be determined, no food had been retained for several days. They were given no food during the twentyfour hour period but did receive salt solution subcutaneously and glu cose solution intravenously. The substances measured in the urine and stools may therefore be taken as describing losses from the body Sodium and chloride from the administered salt solution can probably correctly be included in this statement since the quantities supplied were doubtless less than the deficits which dehydration had produced With the hope of obtaining a urine specimen before beginning treatment, the fluids were not administered until after the first eight hours Catheterization then, however, failed to produce a specimen The infants were thus evidently anume, and the urine secreted during the subsequent sixteen hours may be regarded as a response to the fluids The infants were comfortably immobilized on the metabolism bed and a collection of urine and of stools over the twenty-four hour period was obtained. In order to insure a complete urine specimen, the infants were eatheterized at the end of the period infants (A) vomited a few c c of fluid. With this exception vomiting, which had been frequent before entering the hospital, was absent during the period of study Blood samples were taken at the beginning and at the end of the twenty-four-hour interval

Measurements of total fixed base, sodium, potassium, phosphorus and nitrogen were obtained from both urine and stools. The concentrations of total fixed base, chloride, and carbon dioxide content were determined in the serum of the blood samples, collected and separated under oil

The following methods of analysis were used total base by the method of Fisker, sodium by uranyl zine acetate precipitation as described by Butler and Tuthille, potassium by Fiske's modified cobaltimitrite method in which potassium is reprecipitated as potassium acid tartrater, phosphorus by the method of Fiske and

Subbarows, chloride by Fiske and Lin s method of wet ashing with nitric acid and potassium permanganate and Volhard titrations, carbon dioxide content of the serum according to Van Slyke and Sendroy10 and nitrogen by macro-Kjeldahl,

#### RESULTS AND DISCUSSION

If the loss of body fluid in diarrheal disease caused by failure of reabsorption of gastrointestinal secretions is limited to extracellular fluids and if the quantity of intracellular fluid presenting for ex cretion is determined only by the extent to which body protoplasm is destroyed as a result of the factor of fasting which the situation con tains, the composition of the fixed base exerction in urine and stools can be postulated readily by reference to the diagrams in Fig 1 In other words nearly all of the fixed base in the stools should be sodium and, owing to the sodium deficit thus produced within the body, no sodium should be permitted to enter the urine. The fixed base in the urine should consist chiefly of potassium, the amount of which should correspond to the extent of the destruction of body protoplasm as in dicated by the nitrogen excretion

The measurements actually obtained from the two infants (Tables I and II) extensively disobey these expectations. In both instances the quantity of potassium in the stools is, in relation to sodium, very much larger than would be expected on the basis of the relatively small value for potassium in gastrointestinal secretions and in the extracellular fluids (Fig 1) The urines both contain appreciable quantities of sodium which however, are small fractions of the amounts of sodium supplied by the administered salt solution. The expected considerable excretion of potassium is found. When, however the loss of intracellular fluid calculated from the urine potassium is com pared with the loss of fluid as estimated from urine nitrogen it is found to be much larger These calculated values are given in the third section of the tables \* It thus seems that potassium and a cor responding quantity of intracellular water are excreted in the urine to a much greater extent than can be accounted for by the destruction of body protoplasm as measured by the nitrogen excretion t

The formulas used in calculating the extra and intracellular fluid losses were those of Peters and Van Sb ${\rm Ke}^{\rm st}$ 

 $<sup>\</sup>frac{Na - 0.4.5 \text{ k}}{}$  = liters of extracellular water lost. K = 0.017 Na = liters of intracellular water lost. 112

in which Na and K represent milligram equivalents of base found. As regards the 0.0 value for extracellular water in urine which was found for both intants, it may be noted that the factor 0.425 k. in the first equation produced values for Na from intracellular water of 2.10 m-eq for infant A and 1.23 m-eq for infant B, which very closely cancel the found values for Na given in the table, 1.07 m-eq and 1.25 m-eq respectively

The intracellular fluid loss corresponding to destruction of protoplasm was calculated from the formula

Nitrogen (gm.) x 96 x 76 = c.c. water

Anturers (gain) a set a few and a few account for the excess of excretion of potassium over nitrogen in the urine and stools as available data indicate that the ratio of nitrogen to potassium over nitrogen in sweat is less than that obtaining in protoplasm.

TABLE I

Weight 10 Pounds INFANT A AGED THREE MONTHS Evident Dehydration Fluids Given 10% Glucose Solution, Intra v, 150 c e 09% Salt Solution, Sub a., 200 c c. (== 31 m mol NaCl) Diarrhea and Vomiting Four Days

# Data from Blood Scrum

	N EQ PFR 1	X EQ PER 1	V EQ PER 1	
At entrance	126	212	78	
After 24 hours	142	19 6	06	T

# Data from Urine and Stools

						The state of the state of	a consistent and account the facility of the facility of		
112	,	6 59	1	6 71	1	4 94	-	256	Total
13	22 0	66 0	39.5	178	000	2 97	125	12	Stools
65	310	5 60	27.2	4 93	10 9	1 97	39	181	Urine
MG	M EQ PER 1	M EQ	N EQ PER 1	M EQ	V EQ PER 1	VI EQ	M EQ PFR I	20	
Z	тРО,*	I	ж		Na		FIVED BASE	VOLUME	

\*In terms of base equivalence at reaction of body fluids Pn 7 4

Calculated Losses of Body Water

	", WITHDRAWN",	22.9	34.2
INTRACELLULAR	FROM N C G	20.8	25.2
	FROM K	43.7	29.4
EVTEACELLULAR	FROM Na C O	0 0 14 9	141 N
		Urine Stool	Total

Water trom in-water from in

80.0% Na supplied in salt solution 6.3% Na supplied in salt solution 9.6% Na supplied in salt solution Sodium retention, Sodium loss in urine, Sodium loss in stools,

١

WEIGHT 6 POUNDS. INPANT B. Agen THREE MONTHS.

Diarrhea and Vomiting Six Dave. Extreme Dehydration. Fluids Giyan 10% Glucose Solution, Intra v, 185 c.e. (= 39 m.mol NaOl)

09% Salt Solution, Sub-e,

# Data from Blood Sorum

	FIXED BASE	CO CONTENT	CIITORIDE
	M RQ PER L	M ENG PEER I	א זע דים וידיו
At entranee	116	1	73
After "4 hours	146	136	100

# Data from Urine and Stools

×	λία	299	614	1176
пго	M RQ PRE 1	404	8 61	1
Ē	N 250	2.04	4.37	7.93
K	M RQ PER 1	39 6	47.5	,
	N RO	2 80	9.11	10.00
Na	M EQ PER 1	17.1	67.7	
24	7 IIO	1.25	13 00	14.25
PLYED DASE	M EQ PER 1	22	150	1
TOLUXIE	00	73	192	26.5
		Urine	Stools	Total

In terms of base equivalence at reaction of body fluids Pn 74

# Calculated Louses of Body Water

	' WITHDRAWN '* O.C.	18 0	786
INTRACELLULAR	FROM N	19.6 13.8	÷ 02
	ROM K	25 6	105 0
EXTRACELLUIAR	From Na C.C.	0 0 61 7	61.8
		Urine Stool	Total

Water from h-Water from N

84.0% Na supplied in ealt solution 3.2% Na supplied in ealt solution. 33 0% Na supplied in ealt solution locs in stools, loss in urine Sodium retention Sodium loss in urb Sodium loss in sto simplest explanation of this finding is that, in addition to the release of water from destroyed protoplasm, there occurs a withdrawal of water from tissue cells. The extent of this withdrawal of intracellular water is measured by subtracting the value for released water, calculated from the nitrogen measurement, from the total excretion of intracellular water calculated from the potassium excretion. In the stools the value for "withdrawn" water thus obtained constitutes much the greater part of the excretion of intracellular water, and is approximately as large a quantity as the extracellular water loss calculated from the sodium content of the stools. The total value for "withdrawn" intracellular water in the urine and stools taken to gether is, in both experiments, actually larger than the total excretion of extracellular water.

The measurements obtained from the initial blood serum samples show extensive changes from their normal values for the three quantitatively important structural factors and demonstrate that the process of dehydration has passed the point beyond which the plasma cannot be accurately sustained by water and materials from the interstitial reservoir

The major finding from this study of two infants in an advanced stage of dehydration is the evidence just presented demonstrating that, in addition to the loss of interstitial fluid, which we are accustomed to regard as the essential event, there is operative also a process of withdrawal of intracellular fluid producing a water loss which is quantitatively even larger than the loss of interstitial water

The data obtained from these infants do not explain the process of withdrawal of intracellular fluid. An especially puzzling feature is its removal to a large extent in the stools, which under the conditions of this study, are assumed to be composed of gastrointestinal secretions in which the concentration of potassium has approximately the same small value found in the blood plasma, 50 m eq per liter. In the stools from these infants, the concentration of potassium was for A, 395 m-eq per liter and for B, 475 m-eq per liter The disability of renal function, which is a consequence of severe dehydration, probably somewhat raises the level of potassium in the plasma Direct information on this point is unfortunately lacking. It has been found, however, that in advanced renal disease the concentration of potassium is rarely more than double the normal value The subjects of this study received glucose solution which presumably enabled the kidneys to operate fairly accurately as indicated by the secretion of a sizable volume of rather dilute urine It is, therefore, altogether improbable that potassium accumulated in the extracellular fluids to an extent sufficient to explain directly the high values found in the stools

There is some temptation to suggest a substitution of potassium for sodium by the secretory mechanisms in supporting the required osmolar value of the intestinal fluids. That the total concentration of cleetrolytes was sustained at approximately the body fluid level is shown by the rough agreement of the total fixed base concentration in the stools with the values for fixed base found in the plasma. It is, however, physiologically unlikely that unusual substances could be employed in the construction of secretions and, since these infants received sodium chloride solution, there is little basis for supposing a purposeful or compulsory substitution of potassium and phosphate for the regularly used materials, sodium and chloride

Another conjecture contains, to our minds, some degree of prob ability This consists in premising a much more rapid absorption of sodium than of potassium from the bowel with the result that the potassium content of the stools represents an accumulation derived from the small quantities present in normally constructed secretions In support of this surmise an observation made by one of us may be cited 12 In the case of a normal subject when the food contains sev eral times as much sodium as potassium and, moreover encounters during digestion secretions which contain twenty five times as much sodium as potassium, more potassium than sodium is found in the stools Assuming no reabsorption of potassium, the concentrations of potassium found in the stools of these two infants with diarrheal dis ease describe an approximately tenfold concentration of gastrointes tinal fluids containing, when secreted, the normal value for potassium, 50 m eq per liter Interestingly it may also be seen in the tables that the concentration of phosphate in the stools is closely ten times the value found in normal blood plasma 25 m-eq per liter Since un der normal circumstances there is very little reabsorption of phos phate although potassium is extensively returned to the body fluids, this parallel relationship of the concentrations of potassium and phos phate in the stools of these infants to the normal blood plasma values suggests that diarrheal disease interferes more or less completely with the reabsorption of potassium. In the case of the infant B, whose stool volume was very large 192 cc, a total secretion of nearly 2000 cc of intestinal fluids would be required to account for the ten fold concentration of potassium found. This is a large figure for the secretions but is not of an impossible order of magnitude twenty four hour volume of gastrointestinal secretions for a normal adult is 8-10 liters and the surmise is permissible that the volume of the secretions may be much increased in diarrheal disease. Also, a slight increase in the potassium concentration in the plasma above the normal value which is a not improbable event in severe dehydra tion would greatly reduce the calculated volume of secretions For instance if the plasma potassium in the infant B be taken as 75 m eq per liter instead of the normal value 50 m eq per liter, the volume of secretions required to produce the concentration of potassium found in the stools would be 1200 cc instead of 2000 cc. This explanation of the large exerction of potassium in the stools if it could be estab

lished, would describe a process of withdrawal of intracellular fluid operative whenever abnormal circumstances produce a partial interference with the reabsorption of gastrointestinal secretions

The presence of an intracellular fluid loss complicates our conception of the process of dehydiation and disturbs our confidence in the therapeutic adequacy of parenteral treatment. Since repair solutions must be placed in the vascular or in the interstitial compartment, they cannot contain with safety the intracellular materials, such as potassium and phosphate, at concentrations above the small values pre-The solution devised by scribed for them in extracellular fluids Hartmann contains potassium appropriately to this extent dent, however, that such solutions cannot provide an adequate replenishment of intracellular materials Parenteral therapy has a large. often dramatic, effectiveness It must be admitted, however, that it is not always successful and it may be hoped that recognition of an additional pathologic process in the situation will eventually produce supplementary measures which will provide a more complete control of the severe stage of diarrheal disease

#### SHALMARA

Estimations of the extent and source of losses of body fluid by infants in an advanced stage of diarrheal disease were obtained from measurements of the excretion of sodium, potassium and nitrogen in the name and stools

It was found that intracellular fluid is excreted in both urine and stools to an extent much greater than can be accounted for by 1elease of water due to destruction of protoplasm. The additional water is regarded as withdrawn from tissue cells. The total quantity of withdrawn intracellular water was found to be larger than the loss of interstitial water

According to the findings in this study a loss of intracellular fluid, in addition to a loss of extracellular fluid, must be recognized in the process of dehydration produced by diarrheal disease

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# OBSERVATIONS ON THE EFFECT OF AGING ON THE POTENCY OF SPRAY DRIED ANTISCORBUTIC

HENRY J GERSTENBERGER, M.D., DONALDA N. SMITH, B.S., AND G. L. HACKER, M.D. CLEVELAND, OHIO

A TTEMPTS to protect the vitamin C content of various fruits and vegetables and to obtain it in a concentrated and preserved form have been made rather successfully from the standpoint of retaining a high degree of the potency of the original material by various work crs (Chick, Hume, and Skelton, Givens and Cohen, Givens and McClugage, Harden and Zilva, Harden Zilva and Still, Givens and McClugage, and Harden and Robison)

Givens and McClugage in their experimental study of spray-dried orange juice found that it had retained practically all of its potency three and a half months after manufacture. They concluded their article with the following sentence. 'It is suggested that the dried orange juice will serve as a convenient antiscorbutic for use in infant feeding, on polar expeditions, in the navy, and for soldiers during war.'

This material, however, later on was found to be, in practice, very hygroscopic

Goss in 1925, made a definite statement bringing out this point in his report on orange juice which had been dried by the spraying process two years previously, and which had been found to be still sufficiently potent to cure guines pigs from scurvy in a dose no greater than that required for fresh orange juice

Harden and Robison also referred to the hygroscopic qualities of the concentrated orange suice

This hygroscopic characteristic of orange juice concentrated alone or with cane sugar, represents a severe handicap in the use of dried orange juice as a practical antiscorbutic

Bassett-Smith • in 1920, without particularly commenting on this point, seemingly overcame this difficulty by mixing concentrated lemon juice with lactose and gum tragacanth, putting the material in lozenge form. He found that the antiscorbutic potency of this preparation had been retained at the end of twelve months

The Laboratory Products Company manufacturers of S M.A, being interested at my beliest in making S.M.A. Powder antiscorbutic, finally produced a spray-dried orange juice-lactose combination which was

From the Bables and Childrens Hospital and the Department of Pediatrics of the School of Medicine, Western Reserve University

but slightly hygroscopic. This material was tested in a preventive and in a curative manner on guinea pigs, both at the time of manufacture and thereafter at intervals of one to seventeen months. Material from one of the lots of orange juice dried in this manner was fed to a scorbutic infant fifteen months after its manufacture.

Beginning with 1924, practical experience with the incorporation of the antiscorbutic vitamin in a powdered milk was obtained when, at my suggestion, in the manufacture of Piotein S M A 20 c c of lemon juice per liter of milk were added in the hope of making this mixture antiscorbutic. Protein S M A is a powdered acid protein milk similar to lactic acid and case milks, and has a  $P_{\rm H}$  of 46. This acidity was obtained by adding lemon juice and also lactic acid produced by controlled bacterial fermentation of the milk

In order to be quite certain that a powdered milk to which the antiscorbutic vitamin has been added is in reality antiscorbutic, it is necessary to make observations on its antiscorbutic properties weeks, months and preferably years after its manufacture. Since 1924 six patients with infantile scurvy at the Babies and Childrens Hospital have been fed this material from five to twenty-three months after manufacture. The data obtained on these patients and those on the one human infant and the guinea pigs fed the powdered orange juice described above form the basis of this communication.

### FRESH ORANGE JUICE, SPRAY DRIED AS A CONSTITUENT OF A LACTOSE ORANGE JUICE MIXTURE

In the fall of 1930 two different lots of fresh orange juice were powdered by the spray drying process. That powdered in September has been called Lot No 1 and that powdered in October Lot No 2. Lot No 1 was tested for vitamin C potency both by the preventive and by the curative methods, whereas for Lot No 2 the curative method only was employed.

The powdered orange juice was mixed with water in a manner to make the solution equivalent in content of solids to the fresh orange juice from which it was made. For each test of powdered orange juice, a control group of guinea pigs was fed an identical amount of fresh orange juice. The diet given both groups of animals was one that has resulted consistently, during a most extensive experience covering many years, in the production of a scurvy in guinea pigs that is fatal at the end of three to five weeks after its institution. Both the fresh orange juice and the powdered orange juice solutions were fed daily to the animals with medicine droppers. The curves on the informative charts (Figs. 1, 2, and 3) represent the average weights of the three guinea pigs used in each group

Lot No 1 was packed after drying into small tin cans, the air content of which was not replaced by nitrogen Lot No 2 was placed in

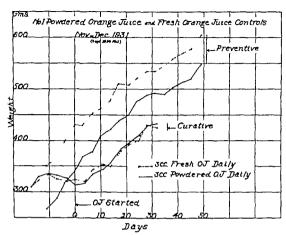


Fig 1.-Guinea plg chart. (O J = orange juice)

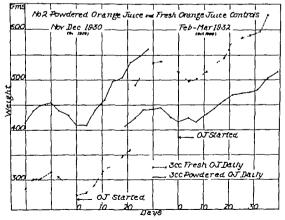


Fig 2.-Guines pig chart.

paper bags which were closed with adhesive tape and placed together in a large ten-gallon milk can, the cover of which was tightly closed It remained in this environment until July, 1931, when it was repacked under nitrogen in small tin cans

Fig 1 shows that powdered orange juice Lot No 1 was as effective as fresh orange juice in preventing and in curing scurvy fifteen months after its manufacture. Inasmuch as the fresh orange juice used in feeding the controls was from a different lot of oranges than that used at the time of drying, this result does not prove that Lot No 1 lost none of its antiscorbutic value. However, we feel justified in assuming that whatever loss occurred was small, and is of no practical significance.

Fig 2 shows that Lot No 2 also retained sufficient antiscorbutic potency to cure the guinea pigs of their scurvy. In the first experiment, made when Lot No 2 was one to two months old, the powdered orange nuice was as effective as, if not even slightly more so than the lot of fresh orange juice used, judging from the angle of the weight curves In the second experiment, made when Lot No 2 was fifteen to sixteen months old, the weight curve of the guinea pigs fed the powdered orange juice was not quite so good as that obtained when Lot No 2 was fed at the age of one to two months considered an indication of a slight reduction in potency that this conclusion is not necessarily correct is shown by Fig. 3, which demonstrates that the curve of the gumea pigs fed fresh orange juice, at the time when Lot No 2 at the age of fifteen to sixteen months was being fed, is practically identical with the curve produced by the latter group of guinea pigs and nearly equally different from the curve produced by the scorbutic guinea pigs while being fed Lot No 2 when it was one to two months old Environmental conditions affecting the animals, probably better than any other factors, can be assumed to have been responsible for this interesting finding

This interpretation is given apparent corroboration by the lapid cure produced by feeding at practically the same time—namely, during January to March—Lot No 2 to a patient with very severe infantile scurvy, in doses equivalent to a total of 45 c c of fresh orange juice per day (Fig 4)

This patient, R K (No 5580), was one year old when the diagnosis of a very severe infantile scurvy was made. He showed the most severe form of scorbutic rosary seen by us (Fig 5). His gums were pathognomonic and the position of his lower extremities was characteristic. He had been suffering from a purulent of this media for some time, and a double mastordectomy had very recently been performed. Drainage was not ceasing and the temperature was not dropping as had been expected after operation. The data presented by Fig 4 show the marked curative effectiveness of powdered orange juice Lot No 2

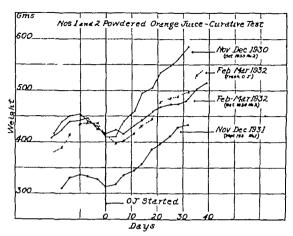


Fig 3-Guinea pig chart

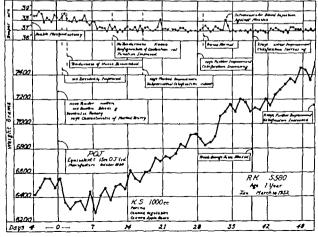
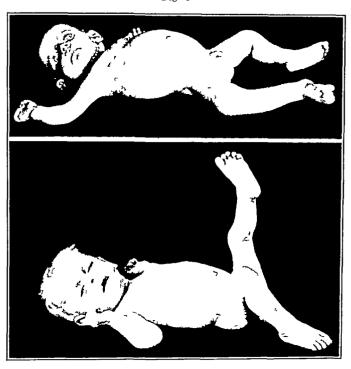


Fig 4.-R. K. No. 5580 (K. S. = Keller's soup P O J = powdered orange juice.)

the administration of which represented the only change instituted in the care of this patient. Fig. 6, presenting a photograph taken twenty-three days after treatment, convincingly shows the improvement in nutrition and in the use of his legs. Fig. 7 gives a photographic reproduction of the roentgenograms of the femure of this patient, taken just before treatment was begun. It presents the well-known changes so characteristic of scurvy. Figs. 8, 9, and 10 (seventeen, twenty-one, and thirty-nine days after therapy) beautifully demonstrate both the

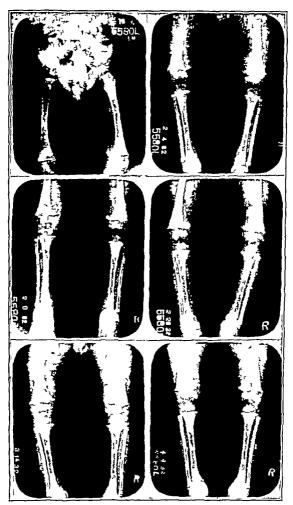




Figs 5 and 6 -R. K. No 5580

extensiveness of the subperiosteal hemorrhages and the therapeutic effectiveness of Lot No 2. It will be noticed in Fig. 10 (thirty-ninth day) that the organized subperiosteal hemorrhages had been reduced in size on the inner sides of the femura and had disappeared entirely on the outer.

At this time the supply of Lot No 2 available for use for this infant was exhausted, and therefore 45 c c of fresh orange juice were administered Fig 11 presents the photograph taken at the end of seventeen days of fresh orange juice administration, and Fig 12 that taken on the thirty-eighth day Figs 11 and 12 correspond in time interval after



Figs. 7 9 21 Figs. 8, 10 1... Figs. 7 1...—R. K. No. 5550

the beginning of fresh orange juice therapy with Figs 8 and 10 for the time interval following the giving of Lot No 2 of powdered orange juice

FRESH LEMON JUICE, SPRAY DRIED AS A CONSTITUENT OF PROTEIN S M A

From 1926 to 1932 six patients with infantile scurvy were fed Protein S M A at the Babies and Childrens Hospital as the only food and as the only source of the antiscorbutic vitamin. Figs. 13 to 18 present informative charts giving diagnostic, therapeutic, symptomatic and prognostic data in detail. The amount of the lemon juice consumed as a part of the Protein S M A is shown at the lower left hand corner of each chait

All of the infants with teeth (Figs 13, 17, and 18) showed characteristically swollen, spongy, bluish red gums (see as example Fig 19, patient RS, No 3911 [chart Fig 17]) The others, of course, having no teeth, were negative in this respect

In each of the six infants a rosary of the bayonet type was present (see as examples Fig 20, patient G P, No 170 [chart Fig 13] and Fig 21, patient R B, No 3774 [chart Fig 16]) That these rosaries were scorbutic and not rachitic in nature can be accepted without question for five of the patients (G P No 170, A S No 774, A Z No 2094, R B No 3774, and R S No 3911) for the following reasons (Table I)

- (1) These patients were fed SMA for many months before the treatment of scurvy was begun. This food in our experience has never failed to cure even the severest form of the regular low phosphorus or low calcium types of infantile rickets.
- (2) The blood serum calcium and the inorganic phosphorus findings were essentially normal and certainly not characteristic of a rickets which would produce so decided a rosary
- (3) Weekly roentgenograms, both at the time when antiscorbutic treatment was begun and during the period of this treatment, showed no evidence of rickets
- (4) The rosaries disappeared in each instance upon the administration of the antiscorbutic therapy instituted and without the additional use of the antisachitic factor beyond that already being administered previous to and during the development of the scurvy (See Fig 22, patient R B, No 3774 [chart Fig 16], showing the effect of seventy days of antiscorbutic therapy begun when Fig 21 was taken)

All of the infants showed somewhere in the osseous system, as studied by x-ray examination, changes that are characteristic of scurvy. The location of these lesions was not uniform in all cases. However, the lower ends of the femula predominated as the region showing the most clear-cut changes. In none of the children were subperiosteal hemorrhages found to the extent shown in patient R. K., No. 5580

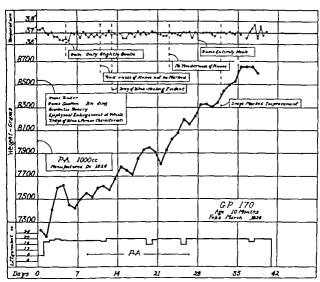


Fig. 12 -G P No 170 (P A = Protein S. M A.)

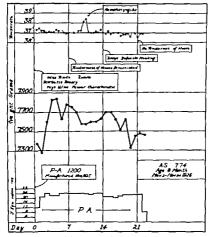


Fig. 14 -- A. B. No. 774

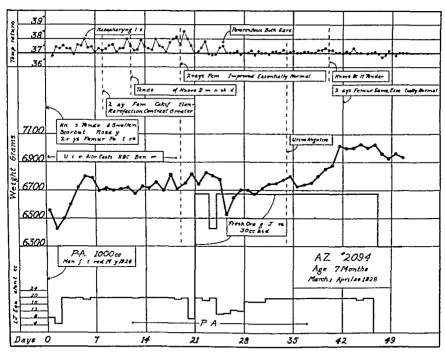


Fig 15 -A. Z. No 2094

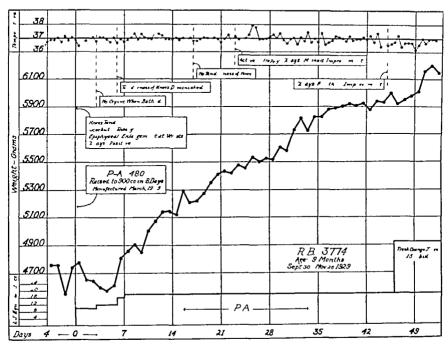


Fig 16-R B No 3774

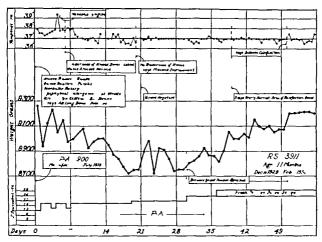


Fig 17 -R. S. No. 2911

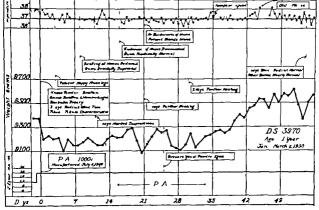


Fig. 18 -- D S. No. 3970

TABIE I

				ΤI	11	ט ע	ioc	R	NA:	יע	ЭF	I	ELL	<b>71</b> E	\TI	νı	כו							
ROSARY PRESENT		Yes Marked scorbutic resary	(Dayonet rorm)				Ves Moderate scorbutic reserv	(hononot form)	(mrot ganofan)	Yes Moderate scorbutic resary	(bryonet form)		Yes Marked scorbutte rosary	(bayonet form)		Yes Moderate scorbutic resary	(bayonet form)		Yes Moderate scorbutic resury	(bayonet form)		Yes Moderate scorbutic resary	(bayonet form)	
ARAY SIGNS OF	MUNDIN FREDRINI	97					No	?		No			$N_0$			No			$N_0$			Νο		
HOSPITAL		11/27/31	to	8/50/37		-	1/3/30	22 /2	3/ 5/30	12/10/29	ţ	3/ 2/30	9/30/59	to	12/13/29	3/ 1/28	ţ	4/20/28	11/ 2/26	to	11/24/26	2/ 8/26	to	3/22/26
ERUM	01 P	100 38		C 10		10.0 4.0	-1	101		110 53			110 49						103 44			97 50		
BI OOD SERUM	DATE	1/19/32		m (1)	01/5		}	20/1/1		2/24/30			07/30/50						11/ 3/26 103 44			2/18/26		
ANTIRACIITIO RECEIVED BEFORE	ADVITSBION	Yes (OX colling	lamp Ward 5	West)			No (mformation	A CALL CALL	doubtint)	Yes (S.M.A.)			Yes (SMA)			Yes (S.M 4 )			Yes (SMA.)			Yes (SMA)	-	
PREVIOUS	DIET	Keller's soup					Milk with	16-11-21	food	S M A			SMA			S.M.A			S M A			S M A		
0.1813		K 5580	1 year	6420 gm			9070	!	1 year 9375 gm	3011	11 months	9260 gm	3774	9 months	4750 gm	1004	7 months	6560 gm	774	8 months	7375 gm	170	10 months	7250 gm
		R. K	$\Lambda g_0$	Wt			0	•	Ago Wt	E 8	Ago	Wt.	R B	Age	Wt	VΖ	Age	Wt	A 8	Ago	Wt.	G P	Age	₩ M

(Figs 8, 9, and 10), in whom the tendency to hemorrhage evidently existed to a very marked degree

A conclusive proof of the scorbutic nature of the pathologic condition of the bone observed is the fact that all of the lesions improved and the bone sconer or later returned to normal solely upon the administration of the antiscorbutic vitamin in the form of Protein S.M.A. (see as examples Figs. 23, 24, and 25, patient A. Z., No. 2094 [chart Fig. 15], and Figs. 26, 27, 28, and 29, patient D. S., No. 3970 [chart Fig. 18])

It is relatively easy to recognize in the roentgenograms early improvement of the scorbutic changes in a bone but it is at times diffi

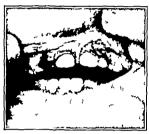


Fig 19 -R. S. No. 2911 (chart Fig 17)

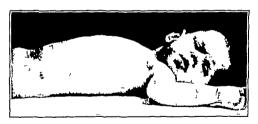


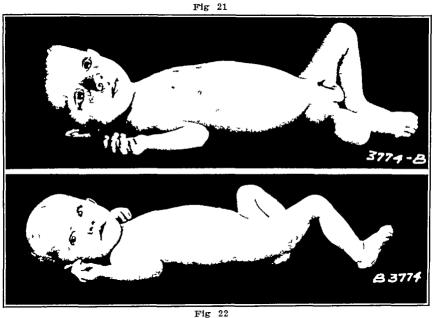
Fig. 20 -G P No. 170 (chart Pig 13)

cult to know when the bone, after the institution of antiscorbutic thorapy has reached a complete restitution to normal. McLean and McIntoshio called attention to this fact in their interesting contribution on 'Healing in Infantile Scurvy as Shown by X Rav''

The roentgenograms of patient A Z show the femurs, first at the beginning of Protein S.M.A feeding (Fig 23 taken March 1, 1928) second seven days later (Fig 24 taken March 8) at which time an increase in the contrast between the excessively calcified line and its adjoining zone of rarefaction had been produced by the treatment, and, third at the time of the disappearance of the rarefled band

(Fig 25, taken March 19, 1928) with an accompanying improvement in the bone structure, eighteen days after the feeding of Protein S M A and three days before the addition of fresh orange juice

McLean and McIntosh¹o also have called attention to this temporary effect of antiscorbutic treatment in augmenting the contrast between the zone of preparatory calcification and the adjoining band of rarefaction (See Fig 24) This contrast between the band of rarefaction and the excessively calcified zone of preliminary calcification is particularly clearly seen in Fig 26, taken Jan 4, 1930 (patient D S, No 3970 [chart Fig 18]) Two weeks later the band of rarefaction (Fraenkel's Trummerfeldzone) has practically disappeared, with an increased filling out and calcification at the lower



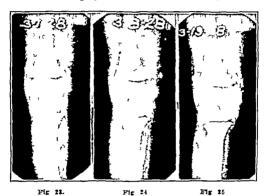
Figs 21 and 22—R. B No 3774 (chart Fig 16)

end of the bone, which on the left side extends slightly underneath the periosteum where probably a hemorrhage had occurred (Fig 27, taken Jan 18, 1930) Ten days later (Fig 28, taken Jan 28) a further decided improvement in the direction of calcification and in contour formation has been made

This very evident improvement in the scorbutic bones of patient D S, No 3970, while coinciding with the disappearance of other symptoms, for instance the swollen gums, was not accompanied by the production of a satisfactory weight curve nor by a normal temperature curve After the taking of the roentgenogram shown in Fig 28 (Jan 28, 1930), 5 gm of brewer's yeast powder were added to the diet three times daily, without any effect on the weight curve,

for this did not rise above its previous level until fourteen days after the administration of the brewer's yeast, at which time, paradoxically, the temperature curve as a result of intercurrent infections became even more abnormal

A very similar experience regarding the delayed return of the weight curve to a normal form, in the face of roentgenographic healing of the scorbutic bones, occurred a few weeks earlier with patient R S, No 3911 (chart Fig 17) to whose Protein SM.A brewer's yeast was added on the thirtieth day after the beginning of therapy, in the hope of improving the weight curve. The failure to obtain a positive result at the end of a week was responsible for the addition of 5 cc of fresh orange juice daily to the Protein SM.A, and pow

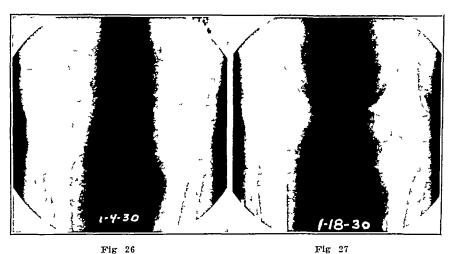


Figs. 22 25 —A. Z. No. 2094 (chart Fig. 15) Fig. 23, taken March 1 1928. Fig. 24, taken March 8, 1928 Fig. 25 taken March 19 1928

dered yeast. While the weight curve rose thereafter it did so in an erratic and unconvincing manner from the standpoint of assuming that the antiscorbutic content of the Protein S.M.A. was inadequate. The previously described course of patient D. S. No. 3970 (chart. Fig. 18), to whose Protein S.M.A. only yeast was added and no or ange juice clearly emphasizes the correctness of this interpretation maxmuch as the weight curve of this patient was just as good as, if not a little better than, that of patient R. S., No. 3911 even after the addition of the fresh orange juice. Both patients were fed from the same lot of Protein S.M.A.

Intercurrent infections, some patent and some occult, in all probability are responsible for the development of this picture in scorbutic infants even though liberal quantities of the antiscorbutic vitamin have been administered and even though specifically scorbutic symp toms disappear (See Fig 15, A Z, No 2094) McLean and McIntosh, 10 who gave to all of their patients the large dose of 90 c c of fresh orange juice daily, have seen patients suffering from infections remain stationary in weight for weeks

Such observations indicate that, while the conclusions of the authors (Aron, 11 Nassau and Singer, 12 Abels, 13 and Stern 14) who have pointed out that dystrophy and dysergy which develop during the so-called latent stage of scurvy are responsible for the development of infections in scorbutic infants, are correct, there apparently are infections of another pathogenesis which develop and continue to persist in scorbutic infants even though the basis for the existence of the specifically scorbutic dystrophy and dysergy has been removed by the administration of the antiscorbutic vitamin in adequate and



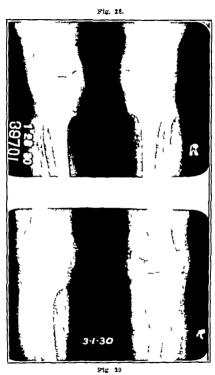
Figs 26 and 27—D S No 3970 (chart Fig 18) Fig 26 taken Jan 4 1930 Fig 27 taken Jan 18 1930

very liberal doses during a sufficiently long period McLean and McIntosh also refer to such cases in their contribution

This is the principal reason, in our opinion, why the weight curves of all of the six scorbutic infants fed Protein S M A did not respond with a rather immediate and continuous upturn, as did patients R B, No 3774 (chart Fig 16) and G P, No 170 (chart Fig 13) Another factor, however, can be accepted as also having played a rôle in bringing about this result, namely, the age and weight of the infants at the time the antiscorbutic therapy was instituted. It will be seen that the infants presenting the best weight curves after the institution of Protein S M A feeding were relatively more underweight for their ages than were those whose weight curves did not do so well

It is clear from careful recapitulation of the data presented by the graphic charts and by the roentgenograms that enough of the anti-

scorbutic power of the 20 c c of lemon juice added to each liter of Protein S M.A at the time of manufacture remained to make it ade quately antiscorbutic, even though periods of from five to twenty three months had elapsed since its manufacture. What might be called the best result was obtained with the Protein S M A used for patient



Figs. .. 8 and 29 -D S. No. 3370 (chart Fig. 18) Fig. 28 taken Jan. 28 1930 Fig. 29 taken March 1 1930

G P, No 170 (chart Fig 13), which was fifteen months old at the time of feeding. The oldest Protein S M.A. twenty three months of age was fed to patient A. Z, No 2094 (chart Fig 15) and, while not so effective, did as well so far as the weight curve is concerned as did the subsequent additional daily administration of 60 cc of fresh or ange juice, a finding which clearly does not warrant the conclusion

that the Protein SMA had lost its antiscorbutic power. As a matter of fact, the healing of the bones as demonstrated by the roent-genograms shows that the Protein SMA did retain antiscorbutic potency

That the antiscorbutic potency of Protein SMA is retained to a satisfactory degree can be accepted from the difference in experience obtained with it and with regular SMA in the feeding of infants. We have never had a patient brought to us with scurvy who had been fed Protein SMA, whereas infants fed regular SMA have been admitted ill with scurvy. This difference undoubtedly is due to the difference in the content of the antiscorbutic vitamin in the two milks

### CONCLUSIONS

1 Fresh orange juice, spray dried as a constituent of a lactose orange juice mixture, was found to retain its antiscorbutic potency in a practically undiminished degree for at least fifteen months after its manufacture

This conclusion was reached upon the basis of observations made on groups of scorbutic guinea pigs and on one very severe case of infantile scurvy

The scorbutic guinea pigs were cured by the daily administration of an amount of the spray-dried orange juice equivalent to 3 cc of fresh orange juice, and the human infant by the giving of a daily dose equal to 45 cc of fresh orange juice

2 Fresh lemon juice, spray dried as a constituent of Protein S M A, an acid protein milk to which are added at the time of manufacture 20 c c of lemon juice per liter, possessed, five to twenty-three months after its manufacture, antiscorbutic potency adequate to cure scurvy in six scorbutic infants, as judged clinically and roentgenologically

The weight curves in the two infants who were decidedly underweight for their respective ages responded with an immediate, decided, and continuous upturn, whereas the weight curves of the four remaining infants who were not so much underweight did not so respond, even though the clinical and roentgenological symptoms of scurvy had disappeared. In two of these four infants additional administration of the antiscorbutic vitamin in the form of fresh orange juice did not alter the weight curve results at the time. Infections that were present in these infants on a nonscorbutic basis were accepted as the principal cause for the irregular weight curves produced

The six infants received daily in the form of Protein S M.A, which was taken as the infants' sole source of food and of vitamin C, at different periods the equivalent of 9 to 24 cc of lemon juice

The lots of Protein S M.A used were made at different periods between the years 1924 to 1930

3 No case of scurvy in infants fed Protein SMA has so far come to our attention. This finding further indicates that Protein S.M.A. is adequately antiscorbutic.

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# DIPHTHERIA IMMUNIZATION WITH CONCENTRATED TOXOID INTRADERMALLY

THE interval between the administration of the last dose of diph-I theria toxoid and the development of immunity is approximately It is true that many children are immune before this three months time1 and also that a number are not immune at the end of this period, as has been amply demonstrated by Schick tests? We have, in this work, attempted to find a means of more rapid active immunization against diphtheria We have tried to profit by the suggestions of Stewart and Rhoads, and by the subsequent work of Brodie and Goldbloom.4 where the superiority of the intradermal over the subcutaneous route in immunization against poliomyelitis was shown Liowenstein's ointment<sup>5 a</sup> and Schick with his intradermal B C G <sup>7</sup> have also demonstrated the efficacy of the dermal route in the production of immunity We therefore determined to test the value of concentrated diphtheria toxoid administered intradermally. The intradermal route has previously been attempted by Gorter and Humniks and Rohmer and Levy<sup>9</sup> who used toxin-antitoxin mixtures, and also by Opitz<sup>10</sup> who used toxin dilutions as well. Through the interest and cooperation of Doctors Fitzgerald and Fiaser of the Connaught Laboratories of the University of Toronto, we have been supplied with concentrated toxoid prepared by precipitation with acetic acid in the cold. This concentrate was of such strength that 02 cc was the equivalent of 1 cc of ordinary toxoid as supplied for general use

A preliminary group of twelve children, all Schick positive, was chosen, and injected intradermally, nine with 0.1 c.c. and three with 0.2 c.c. of this special toxoid. Four of these became Schick negative within six weeks, and one became Schick negative at the end of three months. Four remained Schick positive. Titrations of the antitoxin content of the blood were made in four of this group of twelve children. One child (M.S.), who received only 0.1 c.c. of concentrated diphtheria toxoid intradermally and who became Schick negative within a week, showed three months later a blood antitoxin content of more than ½5 unit per cubic centimeter of blood, which is above the immunity level Another child (H.M.), who became immune at the end of six weeks,

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Read before the meeting of the American College of Physicians, Feb 10 1933

showed also more than  $\frac{1}{12}$  unit at the end of two months. One other child, immunized in two months, showed more than  $\frac{1}{10}$  unit. One child not immunized showed, four months after the injections, less than  $\frac{1}{12}$  unit per cubic centimeter of blood. The ages of these children varied between one and one half and sixteen years, and seemed to bear no relation to their antigen forming capabilities. The details of this first experiment are shown in Table I

TABLE I

NAME	AGE	DOSES	REACTION	POST SCHEEK	INTERVAL	DLOOD AKTITOXIN
M B	6 years	1	3 × 4 0 cm.	Negative	7 days	<40>1/2
H. H	18 months	1	16×1 cm	Negativo	6 weeks	1 10 1 123
им	13 years	1	11.7×2 cm	Negative	6 weeks	<140 >1/2
R.O	11 years	1	)	Negative	6 weeks	1 10 1 123
A. StJ	11 years	1	None	Segntive	6 weeks	
J 8	9 years	2	1.5 × 2.5 em.	\cgative	12 weeks	
JΊ	10 years	1	Very severe	\cgative	5 days	1
aa	16 years	1	1×1 cm	Positive	1 week	j
W H	7 years	1	None	Positive	3 months	
J L.	5 vears	2	None	Positive	4 months	<12.0
A. W	414 years	2	1 em.	Poeltive	3 months	- 7,200
L.PA.	10 years	1	8 x 4 cm.	Negativo	2 months	<34>140

Twelve Schick positiv children, 01 c.c. concentrated toxold intradermally dose repeated in 3 children when first post. Schick was found positive.

This preliminary experiment demonstrated to us that rapid active im munization against diphtheria was possible. We therefore selected an other group of five older children, all Schick positive, and gave these children 0.2 c.c. intradermally of the concentrate (Table II) in a single dose. Four of these children became Schick negative one at the end

TABLE II

				TADUL I	. L		
YAME	AGE	DORES	REACTION	POST	INTERVAL	BLOOD ANTITOXIN	LEMARKS
R. M.	8 years	1	T 104 13×5 cm. desquamated	Neg		Before < 1/200 After > 1/20	
Ir. Ir	D years	2	2.5 × 2.5 cm	1st pos. 2nd neg	8 weeks	,	2nd dose gave severo reaction 5x6 cm Schick neg 7 days after 2nd dose.
1. B	13 years	1	4×8 cm T 103 2	Neg	16 days	>1	
8. R.	15 <b>ye</b> ars		3.5 × 4 cm. severe local	Neg	2 weeks	>1	
JT,	7 years	1		Neg	2 weeks	>1	

Five Schick positive children given 0.2 c.c. concentrated toxold introdermally. One received a second dose when first post. Schick was positive. All immunised.

of seven days and three at the end of fourteen days One child (L L), who was Schick positive at the end of two weeks, was given a second intradermal dose of 02 c.c., and one week later showed a negative

Schick reaction One boy (R M), who became Schick negative at the end of seven days, had a severe local and general reaction with temperature 104° and local crythema 13 x 5 cm. Fourteen days after injection, his blood showed an antitoxin content greater than ½0 unit per cubic centimeter. The other four children all showed a titer of more than one unit per cubic centimeter. We relied on repeated Schick tests to tell us which children were immune and upon the estimation of the antitoxin content of the blood to tell us how much immunity they had developed °

That the Schick test itself, frequently repeated, may be a means of producing an antigenic reaction should be almost self-evident 11 12, 13, 14 The Schick test is done by the intradermal injection of a small quantity of diluted but otherwise unchanged diphtheria toxin, and, in susceptible cases, this quantity is sufficient to produce a local inflammatory reaction which in itself is evidence of antigenic activity. We found, for instance, that by repeating the Schick test in one Schick positive child at intervals of several days, the fourth Schick was negative, and the blood showed a titer above the immunity level. In two other children so treated, the eleventh Schick was still positive in one and the twelfth in the other. Thus, in three children given repeated Schicks, definite immunity was produced in one Flaser, in a private communication, has stated that the mere giving of the Schick test can act as a primary It was evident, therefore, that in order to test accurately the antigenic powers of the intradermal method with concentrated toxoid, the Schick test must be replaced by a method which itself is not For this reason we discarded anterior and posterior Schick tests in some of this work, and determined the state of immunity of the children, before and after moculation, by means of directly estimating the antitoxin titer of the blood serum

We selected a group of ten susceptible children (Table III) as determined by antitoxin titers. Six of these received a single dose of 0.2 c c of the concentrate intradermally. Four of these showed antitoxin contents above the immunity level, one as early as two weeks after injection (M O), two m one month, and one in two months. Two remained nonimmune. Four children, all showing less than ½50 units of antitoxin per cubic centimeter of blood, received two doses of 0.2 c c each, one week intervening. All showed titers above the immunity level, one at the end of eleven days, two at the end of three weeks, and one at the end of twenty-five days. One child given 0.4 c c of the concentrate intradermally in a single dose (the equivalent of 2 c c of ordinary toxoid) showed immunity at the end of one month

<sup>\*</sup>The first series of antitovin titers was made by Dr Donald Fraser at the Connaught Laboratories in Toronto The other estimates were made in the Laboratory of the Children's Memorial Hospital in Montreal by one of us (D L K.)

There is apparently some relationship between sensitivity to toxoid and the rate of the antigenic reaction. Individuals highly sensitive to toxoid (i.e., sensitive to the protein of the diphtheria bacillus toxin) are easily and rapidly immunized 15 those little or not sensitive to toxoid are more difficult to immunize. Forty seven cases studied were divided into four groups according to the severity of the reaction after the

TABLE III

учие	AGE	ALZOTITAL ALZOTITAL	DOSES 0.2 C.C.	REAC TION 18T DORE	REAC TION 2ND DOSE	DIAGOD ANTITOXIV	INTERVAL
G P P R M O M O A. W J Me. J G C B A. C. J B. G	8 years 8 years 814 years 11 years 7 years 7 years 714 years 9 years	<148 > 1/30 <150 > 1/30 <150 > 1/30 <150 > 1/30 <17.30 <17.30	1 1 1 1 1 2 2	em. 0.3 18x1.5 03 3.5x4 0.3 2x9 0.3 0.3	5x4 7x4 7x4 3x7	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	2 months 1 month 1 month 2 weeks 2 months 1 month 25 days 11 days 3 weeks 3 weeks

Second dose given one week after first dose.

administration of introdermal toxoid concentrate (Table IV). Those who had strong local and general reactions three in number, were all rapidly immunized after a single dose given intradermally as were twelve children who had strong local but no general reactions. Nine teen children gave weak local reactions, and of these only 578 per cent (ie, 11) were immunized, while of thirteen children giving no local or general reactions only one was immunized (76 per cent).

TABLE IV

TYPE OF REACTION	NO OF CASES	NO INTIN	IMMURIZED
Strong local and strong general reaction		3	100 %
Strong local reaction	12	19	100 %
Weak local reaction	19	11	57.8%
No reaction	13	1	7 6%

Another point observed in this work is one that has already been recognized by others, namely, that individuals with a moderately high titer—near, but below the immunity level—are very readily immunized, while those having extremely low titers are very difficult and sometimes impossible to bring up to the level of immunity. The same condition has, of course, been observed in the production of antitoxin in horses. Not all of them react in the same way in producing antitoxin. Some are very good antitoxin producers, and others less so <sup>16</sup>. In this same connection, once a child has passed the immunity level it is quite easy to raise the antitoxin content of the blood to a very high titer<sup>17</sup> by one

or two intracutaneous doses of toxoid. Thus a child showing 1/4 unit per cubic centimeter of blood was readily raised to 2 units by a single dose

This work has been but the beginning of a somewhat different approach to the subject of diphtheria immunization in children attempt to develop a rapid method for active immunization, and the work done so far seems to point to the necessity of larger doses, and the importance of the production of sensitivity to toxoid in order to obtain good results It is along these lines that the work is now proceeding So far we have shown that under favorable conditions it is possible to immunize some children rapidly with a single or at most two doses of concentrated diphtheria toxoid, when given intradermally, and that the degree and rate of immunization probably depend upon the sensitiveness of the individual to toxoid

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### MYELOPHTHISIS

## HARRY M GREENWALD, M D BROOKLYN, N Y

ATTIMES it is impossible, from clinical and even from hematologic examination, to differentiate between agranulocytosis, aplastic anemia, and some severe forms of thromboevtopenic purpura. The fever, the ulcerative and necrotic stomatitis or pharyngitis, the granu lopenia, the rapid and fatal course characteristic of agranulocytosis, have all been observed in cases of aplastic anemia. Severe cases of thromboeytopenic purpura have been reported which presented clinical and hematologic findings that could easily lead one to make a diagnosis of aplastic anemia, similarly it is not unlikely that aplastic anemia may be mistaken for thromboeytopenic purpura, particularly in the early stages

In a recent article on aplastic anemia, it was pointed out that there may be some relationship between these three diseases on the basis of bone marrow changes. This idea first suggested itself to me after I had the opportunity of studying the bone marrow in two fatal cases of hemorrhagic purpura and in one case of aplastic anemia. Opportunity has not been afforded me of studying the bone marrow in agranulocytosis, and therefore a description of bone marrow changes in a case of granulopenia in a child five years old, which was recently published by Kato and Vorwald, will be cited

Changes in the circulating blood elements as determined by the usual methods, are in reality indications of disturbances of the hemo poietic system in the great majority of cases, if not in all i.e. diseases of the blood itself do not actually exist, changes may and do occur, but these changes are merely evidence that some disease or disturbance of the hemopoietic system exists. It is obvious therefore that the general term under which agranulocytosis, thrombocytopenic purpura and aplastic anemia are described as "diseases of the blood" is a misnomer, and that a clearer conception of these diseases would undoubtedly be obtained if they were described on the basis of bone marrow changes Dameshek' stated in a recent article that, since the blood platelets are derived from the megakaryocytes of the bone marrow, they should give, in association with the study of the number of reticulocytes and neu trophiles, a complete index as to the activity of the bone marrow this paper the relationship of thrombocytopenic purpura, agranulo evtosis, and aplastic anemia will be discussed from the point of view of bone marrow changes

### ESSENTIAL THROMBOCYTOPENIC PURPURA

CASE 1—D J, a female, was born at full term and normally delivered Several hours after birth petechiae were observed on the skin and on the mucous membranes of the mouth, meconium containing some blood was passed. The capillary resistance test was strongly positive. Examination of the blood revealed the following. The bleeding time was twenty eight minutes, the congulation time, four minutes, there was no retraction of the clot at the end of twenty four hours, the platelets numbered 18,000, there were 4,000,000 red cells and 12,000 white cells, the hemoglobin (Sahli) was 95 per cent. Otherwise the examination was negative. The infant was given 75 cc of whole blood intravenously, this was followed by a cessation of the bleeding from the intestinal tract and a gradual disappearance of the petechiae Examination of the blood on the tenth day of life, the day of the infant's dis

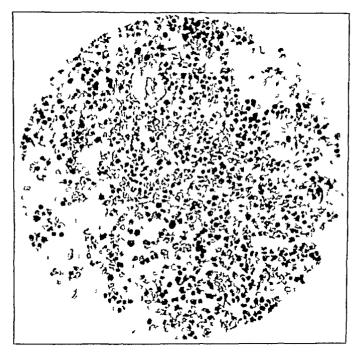


Fig 1—Case 2 Photomicrograph of the bone marrow high power The bone marrow is fairly cellular the majority of cells consist of my electes among which eosinophiles are unusually numerous

charge from the hospital, showed no marked changes from the initial findings. The child appeared well, no petechiae were present, but the capillary resistance test was still strongly positive. Unfortunately no detailed examination of the blood of the parents was made. The subsequent course of this patient's history is unknown.

Case 2—The patient was a newborn male infant who, on the seventh day of life, manifested a purpuric eruption on the face, arms, and trunk, and on the lower extremities. The eruption was bright red, and varied in size from that of a pin head to that of a pea. There were also hemorrhages on the buccal mucous mem branes. Blood was oozing from the circumcised area which had not healed entirely, and from the rectum. The spleen was not palpable. Otherwise physical examination was negative. Only one examination of the blood was made because the child died one and one half hours after it was first seen. The blood report was as follows.

red cells, 6,100 000 hemoglobin (Sahli) 22 per cent white cells 12 000, with 57 per cent polymorphonuclear leucocytes, 41 per cent lymphocytes 1 per cent myelo cytes, and 1 per cent transitionals the congulation time was thirty five minutes, and the bleeding time five minutes. There was no retraction of the clot at the end of twenty four hours. Only 30 000 platelets were present, the capillary resistance test was strongly positive, the Wassermann test was negative.

Necropsy revealed the following The spicen was medium sized firm and dark red the liver was somewhat enlarged and firm and on section, had the appearance of nutmeg the heart was large particularly in its transverse diameter the left reatricle was a mere appendage to the right side of the heart the left auricle communicated freely with the right auricle

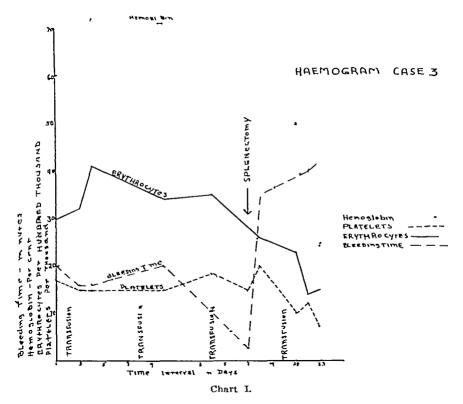
Histologic description of the lone marrow. The bone marrow was fairly cellular with areas of excessive cellularity in which spaces between the bone trabeculae were densely jammed the large sinuses were engorged there were also many red cells in the meshes of the marrow the majority of the cells consisted of myelocytes among which the cosinophiles were unusually numerous mast cells were also fairly common. Among the reticulum cells there were some which stood out because of their unusually large size however they did not show any evidences of excessive phagocytosis. Other cells included mature polymorphonuclear leucocytes lymphocytes normoblasts and cells more embryounl in type which may be classed as myeloblasts or hemocytoblasts. Megakarvocytes were extremely scant and comparatively small. This applied particularity to the nuclei which were conspicuously hyperchromatic. Some of these cells had an oval or bean shaped nucleus which was different from that of the ordinary megakarvocyte. The evtoplasm of some of the cells was scant but in others fairly well developed it stained plain blue and was devoid of the granules usually characteristic of the mature megakaryocyte.

CASE 3 -D N a girl two years old, was brought to me on Oct 6 1931 because of subcutaneous hemorrhages over the entire body and because of spoutaneous bleeding from the mucous membranes of the mouth and nose. The mother stated that the purpuric spots first appeared when the child was three months old, and that at various intervals hemorrhages from the tonsils and from the nose occurred on one occasion there had been bleeding from the ear. Otherwise the past history was negative and unessential. Physical examination revealed purpure spots on the lower part of the abdomen and on the lower extremities. The liver and spicen were not palpable. There was some oozing of blood from the left car and from the right tonsil, the capillary resistance test was strongly positive. Hematologic examination at this time revealed a red cell count of 8,800 000; the platelets were 70 000 hem oglobin (Sahli), 62 per cent bleeding time twenty minutes; congulation time four minutes Whole blood, 50 c.c., from the mother was injected intramuscularly. In tramuscular injections of blood, in varying amounts were given from time to time. For a while improvement in the child was noticed. On January 11 1982 the child again developed severe bleeding from the nose and from the tonsils. Whole blood 40 c.c. from the father was injected intramuscularly, but with no apparent effect on the bleeding Hospitalization was advised.

The child was admitted to the Israel Zion Hospital of Brooklyn on Feb 1 1932. From Feb 1 to Feb 18 four transfusions were given at various intervals, in amounts ranging from 200 to 250 e.e of whole blood. At no time did the child show any improvement. It may be seen from Table I that the platelets were always markedly reduced that the bleeding time was always prolonged and that at no time was there any clot retraction.

On Feb 14 active bleeding from the lips and gums was present and an offusion in the right knee joint was noticed examination of the oyegrounds revealed retinal hemorrhages and blurred discs. A transfusion of 200 c.e. of whole blood was given

on the same day On the next day papilledema was definitely present, and a diag nosis of cerebral hemorrhage was made. Splenectomy was therefore advised. A preliminary transfusion was given and the spleen was removed, the child stood the operation well. Ten minutes after the operation the bleeding time was two and one half minutes, but the platelet count was still only 17,000. The child continued to show evidences of active bleeding, large tarry stools were passed, retinal hemor rhages were even more marked than previously, and there was active bleeding from the mucous membranes of the mouth and from the abdominal wound. On the day after operation the bleeding time was increased to thirty two minutes, and the platelet count to 30,000. On Feb. 20, forty eight hours after operation, the child was again given a transfusion, on this day the platelets were 10,000, the bleeding



time was forty minutes, and there was no clot retraction. On Feb 24, the day of death, the child was practically exsanguinated. Drowsiness and clouding of the sen sorium were present from Feb 14 until the day of death

The necropsy report was as follows The body was that of a white girl, poorly developed and poorly nourished, with marked pallor of the skin and of the mucous membranes. There was a surgical incision in the side, closed with sutures. There was a large collection of clotted blood underneath the dura mater in the occipital region. Both lungs were free and contained air throughout, they were pale, with the exception of the posterior portion of the left lower lobe, which was slightly bluish red and somewhat firm to the touch. The heart was of average size and well contracted. The valves were thin and smooth. Both leaflets of the diaphragm were dark red. Incision revealed a diffuse infiltration of blood within the muscle tissue underneath the peritoneal covering.

TABLE I Blood Findings in Care 3

DATE	2/3/33	2/4/33	3/6/33	7/11/35	2/16/72	1-/14/3-	-1/10/2-	2/_2/33	2/-3/3-	2/24/31
Erythroeytes	3 000 000 3	3,200 000 4,10	1,160 000	4,160 000 3,400 000 3,500 000	3,500 000		2 000 000	2,300 000		1,00 000
Hemoglobin	209	£3	80%	73%	27.5		833	50%		823
Platelets	17 000	15 000	15,000	15,000	18 400	17,000	20 000	10 000		2 000
Bleeding time	20 min.	16 min.	16 mln.	20 mln.		24 min.	ų	40 min.		40 min.
Coagulation time	7 min.	0 min.	3 min	3 min.	_	!	_	10 min		9 nin.
Clot retraction	0	-	6			_	0	•		•
Leucocytes	8,000	9000 ₩		0000			000 +	₩ 600		12 000
Polymorphonuclear lencocytes	65%	250		59%			67%	<sub>2</sub> ئ		St.
Lymphocytes	30%	32%	_	1576		_	27.5	77.77		30%
Eosinophiles	3%		_		_		13			
Monosytes	860	184 1		80	_	_	٤.	ξ. 2	_	72
Transfusions-on 2/2 8/8 2/14, _/_0	0									
Splemeetomy on 2/18										

There was a large amount of clotted blood in the abdominal cavity covering the surface of the intestines. The muscles of the abdominal wall showed similar dark red patches of bloody infiltration as in the diaphragm. The spleen was absent. The stomach contained a large amount of dark red mucous material, and the mucosa was dark brown. The liver was medium sized and pale gravish in color. The cut surfaces showed no traces of the ordinary acinous structure. The kidneys were of medium size, firm, and yellowish gray in color.

Pathologic diagnosis Splenectomy for thrombocytopenic purpura, diffuse intra muscular, intraperitoneal, subdural, and gastric hemorrhages Anemia

Histologic report Bone marrow—the medulla was loose and fairly cellular, many myeloid cells were present, but no megakarvocytes were visible



Fig 2—Case 3 Photomicrograph of the bone marrow high power The medulla is loose and fairly cellular many myeloid cells are present no megakary ocytes are visible

In a discussion of essential thrombocy topenia there are many points of importance, among which is the question of whether there is a congenital form of thiombocytopenic purpura. In the last few years a number of cases have been reported in which newborn infants showed evidence of this disease immediately after birth. (Leschke, Liebling, Waltner, Rushmore, Guttfreund, Dohrn, Greenwald and Sherman') and Case 1 in this paper. The mothers of six of these patients also suffered from the disease. In view of this fact it is likely that there is a congenital or hereditary factor in some of the cases of essential thrombocytopenia. This view is substantiated by the histologic findings of the bone marrow in Case 2 and in Guttfreund's case

Guttfround's patient showed hemorrhages of the skin at birth, and on the second day of life venited blood. Hematologic examination revealed no platelets, a bleeding time of forty minutes, no retraction of the clot and a coagulation time of six minutes. Examination of the mother's blood showed 32 000 thrombocytes. The infant continued to bleed from time to time in spite of repeated transfusions, and died at the age of four months. At necrospy the bone marrow showed many fat cells but no megakary cytes. Although the disease may be congenital, active manifestations may appear only at intervals of weeks, months, or even years.

One of the most distinctive features in purpura hemorrhagica is the change in the quality and quantity of the platelets. Four possi bilities have been mentioned to account for the reduction in platelets The first is the destruction of areas in the bone marrow concerned with the production of megakary ocytes as a result of inveloid hyper plasia, this is probably a mechanism for the reduction of platelets in leucemia and need not be considered in this discussion. The second possibility is the failure of production of merakaryogytes because of bone marrow deficiency with the resulting disappearance or marked diminution of the platelets, changes in the morphology of the mega karyocytes, as for example, the absence of the azure granules, prob ably account for the change in the quality of the platelets. The third possibility is the excessive destruction of platelets in the spleen fourth is that the spleen produces a hormone or some toxic substance which depresses bone marrow function and has a selective action on the megakary ocytes (See Frank,11 Aretz,12 Hirschfeld 12 Klemperer,14 all quoted by Brühl 15)

At first glance it would seem that the question of whether there is a deficient production or an increased destruction of platelets could have been decided by careful studies of the bone marrow and of the In reviewing the literature however it is remarkable to ob serve how few studies of the bone marrow have been made in spite of the fact that a large number of cases of essential thrombocy topenia have been reported Studies of the bone marrow have been made by Lautier Oberling and Worringer 16 Forster 17 Frank, 11 Kaznelson, 18 and Wiener 18 All the authors mentioned found large numbers of megakaryocytes except Lautier Oberling and Worringer, who found an absence of megakaryocytes in a boy five years old who died one week after splonectomy-a case similar to Case 3 Stern and Hart man, 20 however, found definite morphologic changes in the megakar yocytes on sternal puncture particularly an absence of azure granules In two of the cases here presented examination of the bone marrow showed no megakary ocytes in one and only few megakaryocytes with morphologic changes in the other In neither of these cases was there any evidence of excessive destruction of platelets in the spleen While it is difficult to draw definite conclusions from three or four cases, it is not illogical to assume that the thrombocytopenia in some cases of purpura hemorrhagica is based on a deficiency of the bone marrow which may well be congenital

Kaznelson<sup>18</sup> recommended splenectomy for the cure of essential thrombocytopenic purpura because of his belief that the thrombo cytopenia is due to a primary hyperfunction of the spleen with an increased destruction of the platelets. Since then many reports have appeared substantiating the excellent results obtained by Kaznelson with splenectomy Occasionally, however, cases have been reported that did not respond to splenectomy, for example, McLean et al,21 Kasdoba,22 Lautier, Oberling and Worringer,16 Blumfield,23 Jones and Tocantins.24 Case 3 in this paper. In studying these reports one is impressed by the fact that the failure with splenectomy occurs in very young children Piney25 has divided the results of splenectomy into three groups The first is that in which there is a rapid and persistent rise in the platelet count to normal figures, the second is that in which there is a rise after operation, but a drop later, and the third is that in which there is no increase in the platelet count, such as This substantiates the belief that has lately beoccurred in Case 3 come prevalent that the platelet count alone should not be used as an indication for the removal of the spleen

In view of the foregoing, is it not possible that each of the three oninions may be correct at one time or the other, namely, first that there is a deficient production of platelets because of a congenital inferiority or insufficiency of the bone marrow, second, that there is an increased destruction of platelets in the spleen, and third, that the spleen inhibits the production of platelets. In other words, it is not improbable that there are two types of thrombocytopenic purpura The first occurs in infants who are born with a deficient bone marrow. which in itself is not enough perhaps to produce active manifestations of the disease, and that some toxic or unknown agent, which has no effect in a child with normal bone marrow, produces the typical picture of purpura hemorrhagica The patients belonging to this group will not respond to splenectomy In the second type the bone marrow functions normally, i.e., a normal number of megakaryocytes of good quality is produced, but the platelets are destroyed in the spleen itself, or, as Frank11 believes, the function of the bone marrow which was previously normal, becomes depressed or inhibited by some hormone or toxic substance produced by the spleen It is in the patients of this group that the brilliant results from splenectomy are obtained

In both groups the toxic agent which is the exciting factor probably has a destructive action at the same time on the capillary walls producing increased permeability which is mainly responsible for the spontaneous bleeding. This view probably explains the findings of

many observers that there is no relationship between the severity of the disease and the platelet count. As a matter of fact, it is Brühl's16 opinion that the most important factor in the production of active bleeding in purpura hemorrhagica is the increased permeability of the capillaries This opinion was also expressed by Jones and Tocantins 44 who stated that capillary hyperpermeability or capillary weakness is essential for the production of hemorrhagic phenomena which may appear if this condition is present alone or if both capillary hyper permeability and platelet desiciency are found. On the other hand, Lescher and Hubble2s stated that the relative importance and the possible interaction of platelet and capillary in the production of hemorrhages are not fully settled. They point to the fact that in creased capillary permeability cannot be the primary cause of hemor rhage, since such blood disorders as aplastic anemia, in which there 18 simply a bone marrow deficiency with diminished production of the blood elements, show no suggestion of capillary affection. Finally, it is suggested that bone marrow punctures be made in cases of throm bocytopenic purpura to determine the presence or absence of mega karvocytes

### AGRANULOGY TOSIS OR GRANULOPENIA

Agranulocytosis is uncommon in childhood Recently Kato and Vorwald's reported the case of a female white child, five years of age, who appeared acutely ill and moderately emaciated when first seen The posterior pharyngeal wall had some small ulcers surrounded by a dirty exudate, ulcers of the mucous membranes were also present on the checks and under the tongue, the cervical glands were not en larged Otherwise physical examination was negative except for the presence of a pneumonic process over the left lobe posteriorly child was under observation from May 30 1931 until death, which occurred on June 2, 1931 The most characteristic abnormality was the blood picture which showed a leucopenia ranging from 550 to 900 white cells Only on the day of admission were granulocytes seen The differential count on this day was Neutrophilic leucocytes, 1 6 per cent, eosinophiles, 0 basophiles 08 per cent, myelocytes 08 per cent, lymphocytes 96 per cent On the two subsequent days of the child's stay in the hospital no granulocytes were observed Ervthro cytes ranged in number from 3,250,000 to 3,750 000 The hemoglobin (Newcomer) content was 51 to 56 per cent The platelets were 170,000

These authors differentiated essential agranulocytosis from symp tomatic agranulocytosis and stated that while the former is rare, only five cases having been reported up to the time their report was published the latter is common. The bone marrow in their patient showed but slight activity, all the elements found were mainly hemocytoblasts, the mature myelocytic elements were scanty, occasionally

a promyelocyte was found, but myelocytes, mature basophilic, eosinophilic, and neutrophilic leucocytes were almost entirely absent Megakaryocytes were fairly numerous

Kastien<sup>27</sup> stated that the symptomatic type, in which evidences of a severe infective process are usually found, is due to a peculiar specific reaction of the bone marrow to a toxic agent. Harkins<sup>28</sup> also divides the cases into two groups, as follows

- 1 Primary granulopenia
- 2 Secondary granulopenia, due to
  - a Chemical poisonings
  - b Radiation
  - c Sepsis
  - d Blood diseases-aleucemic leucemia, aplastic anemia

He concludes his classification, however, with the statement that it is possible that eventually all cases will be considered secondary

Recently Weiss and Goldbloom<sup>29</sup> described a symptom complex somewhat similar to that described by others as agranulocytosis, which they termed dysplastic granulocytemia. It is characterized by a primary involvement of the granulopoietic system with the resultant production and distribution of imperfectly constructed neutrophiles.

The points that are still open to question, as far as classification and etiology are concerned, are First, is granulopenia a primary disease due to an unknown virus or to a toxic agent associated with the Benzene ring (Kracke³o) with specific affinity for the myeloid system, or second, is it a syndrome which may occur in the course of any septic process when toxins attack the bone marrow, the resulting symptoms depending on the duration and the intensity of the toxic agent, or third, is there some endogenic factor, for example congenital weakness of the bone marrow, at fault and would a toxic agent which produces no effect on the myeloid system in a normal individual produce granulopenia with all its severe manifestations in an individual with a congenital deficiency of the marrow? The fact that some patients present a previous history of leucopenia, as was recently reported by Harkins,³¹ would speak for the last viewpoint

The points that are well established and that should be emphasized are. First, that the decrease in the granulocytes in the blood is due not to excessive destruction in the circulation but to deficient production in the bone marrow, body defense is lowered because of the marked decrease or absence of leucocytes in the circulation, which fact accounts for all other manifestations including the necrotic lesions of the mucous membranes. Histologic examination of the bone marrow at necropsy or examination of the bone marrow during life (Kastien<sup>27</sup>) shows quite regularly a cell poor marrow with practically no granulocytes. This is true of both groups of cases. Fitz-Hugh and

Krumbhaar, 22 however, reported one case of agranulocytosis with mycloid cell hyperplasia in the bone marrow

In other words, regardless of whether the disease is primary or not, or whether an infective process can be demonstrated or not, the disease or syndrome does not occur unless a deficiency of the bone mar row is present. Whether this deficiency is based on a congenital, weak my elopoietic system or not is a problem which does not lend itself to solution at the present time. It is obvious therefore that the terms "granuloguma" are mismomers and that each term describes but a single phase of the disease.

### APLASTIC ANEMIA

It is now generally conceded that aplastic anemia is a disease sur generis and is not a biologic variation of some form of primary or sec ondary anemia The disease is characterized by its rapidly and pro gressively fatal course in no true case has the patient been known to recover. The two outstanding features of the disease are the severe anemia and the hemorrhagic diathesis which manifests itself by hemop tysis, epistaxis and purpuric eruptions. The blood picture is of course the main point of clinical diagnosis. There is a marked de crease in the hemoglobin content with a diminution of the red cells to a million or less, the hemoglobin is reduced to 10 or 15 per cent the color index is approximately 1, nucleated red cells reticulocytes and polychromatic erythrocytes are absent, there is a decided leucopenia with a reduction of the neutrophilic leucocytes and an almost com plete absence of eosinophiles Thrombocytopenia is constant and is a feature of the disease

There are two types of aplastic anemia—first, the primary or essential—and second, the symptomatic—In this paper only primary or idiopathic aplastic anemia is discussed—The most generally accepted explanation is that the disease is due to a primary lesion of the bone marrow—Frank<sup>11</sup> expressed the opinion that the disease results from a primary aplasia of marrow by some unexplained toxic action on the marrow itself and that there is a simultaneous disappearance of eryth rocytes granulocytes, and platelets—This theory explains his preference for the term 'panmyelophthisis'

Hirschfeld,<sup>12</sup> Pappenheim <sup>23</sup> Türk,<sup>14</sup> and Nageli<sup>25</sup> are of the opinion that aplastic anemia results from a congenital or acquired deficiency and that any sort of infection or intoxication produces the symptoms characteristic of the disease. The following case<sup>1</sup> briefly cited here bears out this opinion to some extent. The disease appeared to be initiated by the advent of an upper respiratory infection and aggravated by one dose of toxim antitoxim.

### REPORT

S B, a girl of Jewish extraction, was born at full term and normally delivered She was well until sixteen months of age, when she had an attack of tonsillitis. On Feb 9, 1932, immediately following the attack, the mother noticed that the child looked pale and, on the advice of her family physician, sent the child to a hospital where it was found that the hemoglobin content of the blood was 31 per cent. A transfusion was given, and the child was discharged several days later as improved. The child was apparently in good health until May 15 when an injection of toxin antitoxin was given. This was almost immediately followed by an elevation of temperature to 102° F, and the arm, at the site of the injection, became red and swollen. The mother noticed a change in the color of the patient and said that the skin was a muddy brown. The child was then readmitted to the hospital for treat

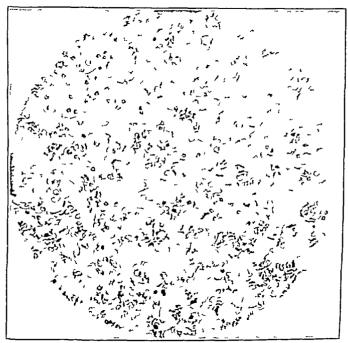


Fig 3—Photomicrograph of the bone marrow high power The meshes of the reticulum degenerating red cells one megakaryocyte and a few other cells mostly lymphocytes.

ment and another transfusion was given. The general condition, however, became worse and, against the advice of her physician, the patient was removed to her home. At this time, June 5, I was asked to see the child. Examination revealed a sick child whose sensorium was clear, but who was apathetic. The skin had a dirty brown appearance, but the lips and finger nails were almost white. The conjunctiva and the mucous membranes of the mouth appeared bloodless, an ulceration of the pillar of the left tonsil which bled rather freely was present. Petechiae were present over the flexor surfaces of both arms, the capillary resistance test was strongly positive. Examination of the blood showed the following red cells, 750,000, hemoglobin (Sahli), 10 per cent, white blood cells, 22,000, of which there were 8 per cent polymorphonuclear leucocytes, 80 per cent lymphocytes, and 12 per cent lymphoblasts. The platelets numbered 25,000, there was one reticulocyte in 2,000 red cells, the bleeding time was ten minutes, and the coagulation time four minutes.

The patient was given 200 e.c of whole blood intravenously on several occasions. She was fed fresh bone marrow first by gavage and later by mouth. Temporary improvement occurred so that there was a distinct remission in the disease which lasted about two months. On Sept 7 the patient was readmitted to the Israel Zion Hospital of Brooklyn in a moribund state. In addition to the evidences of a severe anemia there were signs of consolidation of the lower lobe of the left lung. On the following day the child had a convulsion which lasted affect minutes this was followed by come which persisted until death on the same day.

Examination of the blood on the day before death Sept 7 showed the following red cells, 1700000 hemoglobin (Sahli) 30 per cent leucocytes 6000 with 1 per cent polymorphonuclear leucocytes 89 per cent lymphocytes and 10 per cent lymphoblasts. There were 20000 platelets, and 1 reticulocyte in 1000 red cells.

A complete necropsy was performed but only the bone marrow findings will be cited here. The bone marrow in the sternum was dark red, and when the bone was cut, much blood cozed out the marrow of the tibin was abundant dark red, and quite firm. Histologic examination. The marrow in the long bones, as well as in the ribs, showed enormous congestion with red cells while between the vessels edema was prevalent. In addition to the endothellal cells lining the blood vessels only scanty cells were present most of which were polymorphonuclear leucocytes. There were also occasionally large cells of the size of megakuryovetes with one single oral or irregularly shaped nucleus. Many of the polymorphonuclear cells seemed to be degenerating. There were also a few reticulum cells with normally shaped nuclei. Myclocytes were found in places but they were much less numerous than the polymorphonuclear cells.

The most constant and striking pathologic change in aplastic anemia is a fatty yellow appearance of the bone marrow. The presence of a red bone marrow, however should not lead one to discard the diag nosis of aplastic anemia until careful histologic study has been made. In this patient, while the bone marrow appeared red on gross examination microscopic examination revealed that this color was due to hemorrhage and that there was an almost complete absence of cellular elements.

That an acute infection may be the starting point of the disease has been observed by several authors (Smith 26 Greenwald). It seems, however, that some other factor must be concerned in the pathogenesis of primary aplastic anemia or many more cases would occur. It is not unlikely that a congenital inferiority of the bone marrow is present from birth, and that an infection or a toxic substance which in a normal person would produce only mild and temporary changes in the bone marrow, is sufficient to bring about the severe, permanent, and more or less widespread changes characteristic of aplastic anemia. Changes in the blood picture pointing to an insufficiency of the bone marrow have been found in other members of a family in which the disease occurred (Bickel 27)

Thus it is evident that definite bone marrow changes are present in these three diseases and that deficient production of one or of the other or of all the blood elements normally produced by the marrow is encountered. Lescher and Hubble<sup>26</sup> suggested that each element

has its appropriate regulator, but the fact that intermediate cases occur makes it equally certain that the regulatory factors are not rigidly selected for only one element They believe that the deficiency in the bone marrow occurs because of a deficiency in the controlling This point of view is purely hypothetical, as is the point of view expressed in this paper, that aplastic anemia, agranulocytosis, and some forms of thrombocytopenic purpura occur primarily because of a congenital defect of the bone marrow Further investigation may leveal the accuracy or fallacy of one or of the other or of both of these hypotheses So too, the question as to whether these three conditions are distinct and separate diseases or whether they are closely related and are possibly variants from an identical origin does not bear discus sion because of our limited knowledge. A fact that is not hypothetical and that is worthy of emphasis is that the three diseases resemble one another in the clinical and blood pictures, and particularly in the bone marrow changes

The difficulty that arises in classifying diseases when the nomenclature is based only on one sign or on one symptom may be seen from the following Bigler and Biennemann,38 in their report of a series of cases of agranulocytosis, included a number that were unquestionably cases of symptomatic aplastic anemia. In six cases there was a simultaneous and gradual reduction of red cells, platelets, and granu Indeed the authors stated that their cases seemed to coincide in clinical course and in blood picture with the group classified as aplastic anemia, but the fact that the bone marrow was red instead of yellow caused them to abandon the diagnosis of aplastic anemia The error of such a conclusion has been pointed out by several authors (Baar and Stransky, 39 Greenwald, 1 and Lindquist 40) That Bigler and Brennemann were cognizant of the fact that the present classification leaves much to be desired and that there may be some relationship between the diseases may be seen from their conclusion in which they stated "From a study of our cases and of the literature it seems that there is no one etiologic agent that can produce the condition decribed here, but that any one of several by their action may produce a similar condition, varying as to clinical picture and to blood picture according to the part of the hemopoietic system affected, the erythrocytic and granulocytic, the lymphatic or thrombocytic "

Whether each bone marrow element has a special regulator, as Lescher and Hubble<sup>26</sup> believe, or whether one or several etiologic agents operate to produce these diseases, the fact remains that a nomenclature based on pathologic changes is certainly more desirable than one based on a single sign or symptom. It seems to me that the term "panmyelophthisis" for aplastic anemia, as Frank<sup>11</sup> originally suggested, and the terms "granulophthisis" and "thrombophthisis" for agranulocytosis and thrombocytopenic purpura respectively, as

Lescher and Hubble<sup>20</sup> suggested are to be preferred to the present terms. It is also suggested that the term 'thrombolytic purpura,' first employed by Karnelson be adopted for the cases of thrombo cytopenic purpura in which the reduction of platelets is due to an increased destruction by the splcen. For the differentiation of these two types of purpura bone marrow puncture as suggested before, is necessary

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### FETAL AND NEONATAL MORTALITY

### CLIFFORD G GRULEE, M D CHICAGO, ILL

THIS age-old subject has been discussed and argued over until it is worn threadbare and yet it seems to me that there is still something to be said about it During the last few years and especially since the White House Conference, there has been a renewed interest in the newly born infant, and in attempts to reduce neonatal deaths It is therefore, perhaps not untimely to consider again the question of mortality before and just after birth With the experience which we have had within the past two decades in the reduction of mortality in infants past this age, we are likely to think that the approach to the problem in the newborn and fetus will be just as easy and the results to be obtained will be just as striking Perhaps no method of approach to this subject is better than that of a consideration of the causes of our failures in those periods of existence Certainly we must confess that we approach the subject of reduction of mortality at this stage of development with much less knowledge of disease and of life processes than that which we possess for the older infant, no matter how madequate that may be

Inheritable factors in the wide sense of the term have much to do with disease as we see it in adults and in children. Certain conditions and certain differences can only be accounted for on this basis Why, for instance, two children growing up under practically identical conditions should differ as to hemoglobin content in their blood is one of the things which can only be accounted for by presupposing a fundamental and inherited difference in the iron metabolism of the That this factor plays a very definite rôle in the two individuals mortality of the fetus and newly born child has received comparatively That this rôle may be of varying degree is a thing scant recognition which has scarcely been considered Let us attack this problem then First, the inherent inheritable factor and secfrom two standpoints ond, noninheritable factors which have to do with disease and trauma We must always remember that to draw a sharp line between the two is impossible. Inherited predispositions will invariably have an effect upon disease and to a certain extent upon trauma trauma may, on the other hand, be determining factors too, when inherited taint plays a predominant rôle A statement of Streeter in a recent monograph sums up these ideas

"It is now well known that eggs, and by eggs I refer to fertilized ova, are not all of equal quality. In pigs and in man it is estimated

that as many as 25 per cent of them are not good enough to be born as living individuals. The failures are found in the uterus arrested in various stages of development in proportion to the degree of their poor quality. In man such specimens make up a large part of the material that the physician encounters in miscarriages. Nor is the importance of quality limited to uterine life. Whether the infant survives its first year—and in fact a large number of them fail to do this—depends in considerable part on the original quality of the egg. If they withstand the usual experiences of life until between 50 and 60 years and then succumb to its aggregate wear and tear, they con form to the actuary a expectation of life at birth, and to the embry ologist's expectation to the performance of an egg of average quality. It is only the extraordinarily good egg that is still going strong at 80 years, and we see him (or her) do this in the absence of any exquisite hygienic regime or environmental favor."

Let us approach this subject from the standpoint first, of fetal deaths and then of aconatal deaths. In a recent article by Gillespie the cause of death in 338 cases of stillbirth is discussed and I am repeating here the table (Table I) which is contained in that article So far as I know this is the most recent attempt to discuss this subject and while there may be many others there is no particular advantage in a large mass of statistics. Slight variations of course may be expected, but the main causes of fetal deaths remain very much the same and for the purpose of this paper we are not so much interested in minor changes as we are in large groupings.

If we divide the groups under the two headings mentioned above we shall find that under the first heading or the inherited factors, the following will unquestionably come

Prematurity	54 cases	15 97%
Malformation	37 cases	10.94%
Fetus Papyraceous	1 caso	0.29%
Oligobydramnios	1 caso	0.29%
Introutering dooths (macerated)	54 cases	15.97%

This makes a total of 147 deaths (43 46 per cent)

Those belonging to the second category may be mentioned as—

Syphilis	18 case	s 5.82%
Prolapse of the cord	9 case	s 2.06%
Trauma at birth	101 ense	s 2988%
Difficult labor	° case	s 0.599∕s
Asphyxia	1 ense	0.29%
Moningitie	1 case	0.29%

This makes a total of 132 deaths or 3903 per cent. In other words the conditions which are frankly to be classed in the inheritable causes are greater than those which are to be classed in the non inheritable causes. Of the total number of 338 cases of death, in 13 the cause was undetermined. This leaves a balance of 46 which were

Table I Causes of Drith in 338 Cases of Stillbirth (Gleiespie)<sup>1</sup>

					   			AGF,	MONTHS			
CAUSE OF DEATH	NI VLES	FEMALES	TOT VI	Per cent	LESS THAN 5	56	6.7	7.8	8.9	9 10	10 AND MORE	UN KNOWN
Stillbirth	180	158	338	-	1	10	75	<u>6</u>	43	59	101	94
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Toxemia of prognancy	9	6	10	4 43	;	ł	-	-4*	۳.	٠.	က	
Placenta previa	7	2	11	3 25	;	!	;	ļ	ေ	¢1	ۍ	Н
Abruptio placentae	G	က	12	3 55	;	;	1	CJ	-	-+	<del>-1</del> "	<b>,</b> 4
Prolapse and compression of cord	<del>-j+</del>	ເດ	<b>6.</b>	5 66	¦	!	Н	;	Н	ಣ	7	!
Prematurity	33	21	<del>1</del> 9	15 97	-	က	16	13	12	<b>C</b> 3	ļ	တ
Past maturity	C.3	<b>C</b> 3	4	1 18	;	!	;	;	1	;	4	;
Trauma at birth	54	47	101	20.88	;	г	ŗ	Σ	တ	18	61	~
Malformation (congenital)	15	61 63	37	10.94	ł	Н	တ	2	រះ	Ľ	က	ø
Vaginal bleeding (cause unknown	C1	¢1	-7	1 18	;	I.	<b>c</b> 3	;	ţ	-	;	П
Difficult labor (cause not given)	1	<b>c</b> 7	<b>c</b> 3	0 29	;	;	}	;	;	_	-	ł
Asplyvia (cause undetermined)	П	;	۲	0 29	1	;	;	1	ļ	-	;	ł
Moningitis (focal)	;	-	-	0.29	;	;	!	;	ţ	Т	;	;
Fetus papyraceous	;	-1	-	0 20	;	l I	;	!	;	¦	ł	<del></del> 1
Oligohydramnos	-	;	Н	0 20	;	1	1	Н	1	ļ	;	
Intrautorino death (macerated)	31	63	Z,	1597	;	ro	¢1	2	9	G	c	16
Undetermined	۲-	9	13	3 84	1	1	¦	П	¦	¢1	7	· •

due to the following causes toxemia of pregnancy, placenta previa, abruptio placentae and vaginal bleeding. It is extremely difficult to place these 46 cases in either category, but in all four of them, there is likely to be an inherited factor.

Let us take up these items singly and see in the present state of our knowledge which are likely to respond to preventive measures. First, prematurity. In the analysis of the causes of premature birth it is demonstrated that in a large proportion of cases the cause of the prematurity is unknown. In a certain small proportion syphilis is to This varies in different statistics but nearly every one will agree that in most communities it offers but a small percentage of cases of premature birth and therefore is not a large factor lis, however is capable of treatment and presents the most hopeful prospect with which we have to deal in the reduction of fetal and neo natal mortality Trauma occasionally has been regarded as a factor in prematurity but there seems to be some question as to whether in those cases it is the single factor. Certainly the same trauma does not produce the same results in two individuals. In other words, trauma may be the exciting cause, but there may be also an inherited predisposition to prematurity which results in the birth of the child before term from very slight trauma. Disease in the mother is a factor in production of prematurity. For instance during the epidemic of influenza in 1918, abortion was the rule in women who were preg nant at the time of infection and it is a well known fact that other infections may be the cause of abortion. Not only infections but gen eral diseases such as nephritis, severe heart disease, severe diabetes exophthalmic goiter, etc., may play a rôle. But, even after we have taken into consideration all these causes, it still remains true that the vast majority of cases of prematurity are from causes unknown all probability this group represents some defect in the egg and is the result of some aberration in mating, the nature of which, or the natures of which, we do not know There need be no discussion of the second group that of malformations These are recognized as a disturbance of inheritance and therefore come definitely within this group The same may be said of fetus papyraceous oligohydramnios and likewise of intrauterine death (macerated fetus)

When we take up the group which has to deal frankly with the second category syphilis is mentioned first. There is no question but that if syphilitic mothers be properly treated during pregnancy, the majority of infants will be born at term and viable. This group which constitutes about 5 per cent of the cases in Gillespie's table can in large part be saved. The second item, prolapse and compression of the cord is a serious complication of labor as a rule though each may possibly be overcome by obstetrical procedures. The third item, trauma at birth, I shall take up more extensively in the discussion of

Table I Causes of Denth in 338 Cases of Spillebryh (Gillespie)<sup>1</sup>

FEMALES TOTAL
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selves as a rule not incompatible with life the congenital defects which affect the vital organs of the body frequently are Nearly all those conditions affecting the brain such as anencephaly, hydroceph alus, hernia cerebri are fatal in a short time. Congenital brain de fects may not be fatal but the condition is such that the individual is as a rule of no value to society. Defects in the gastromtestinal tract are frequently incompatible with life such for instance as esophageal atresia, duodenal atresia congenital absence or atresia of the bile ducts and anal atresia Some of the minor congenital defects such as Meckel's diverticulum may to undiagnosed causing no symptoms throughout a long life Congenital defects of the lungs especially congenital atelectasis are often incompatible with life other congenital conditions such as convenital cyst of one lung may exist for some time without causing death of the individual of the heart of a congenital nature are frequently the cause of death at this age but it is surprising how defective a heart may be and the individual still survive. I know of no statistics that will tell us what proportion of cases of congenital heart disease succumbs in the first few days of life. The genitourinary defects are rarely incompatible with life at this age. Frequently they will respond to surgical treat ment. It is very evident that a large proportion of the congenital defects is necessarily fatal in the first few days of life even if the child be born alive

As to birth injuries Those of chief importance are the intraeranial injuries which will be taken up later, together with intraeranial injuries which cause death of the fetus. The other birth in juries are usually of minor importance or associated with those of the brain. Occasionally rupture of the liver or hemorrhage into the suprarenal capsule may be the cause of death, but these conditions are essentially unusual

For our purpose it is of no special value to go into the question of infections. Certainly infections that occur immediately after birth should be prevented. Occasionally it is difficult to prevent infections, such as meningitis, but there is very little excuse for the generalized infections of a septic nature which occur as a result of lack of proper asers is or antisensis at the time of birth.

When we come to the question of diseases peculiar to the newborn, an analysis is very enlightening. In almost none of them have we any adequate idea of etiology. Hemorrhagic disease of the newborn from the etiologic standpoint is still an enigma. Those cases of interus gravis which are not associated with infection are likewise of unknown cause. Idiopathic anemias and generalized edema have so far not been associated with any definite etiologic factor. Winckel's and Buhl's diseases are probably associated with infection. At any rate they are so unusual as to be of little importance in a consideration

of the causes of neonatal deaths. Conditions which cause death in children of later age, such as, bronchopneumonia, nutritional disturbances, etc., are not usual at this time, and may be left out of our calculation. If we look over this list, we find that there is a fair proportion of these children which we can reasonably expect to save even with our present limited knowledge. Even the cases of congenital defects are not hopeless with respect to life. In many instances operative procedures, while extremely hazardous may at times prove life-saving. Those conditions which affect the brain, however, are nearly always fatal or worse.

There is very little reason why we should lose any large proportion of newborn infants from infections. It is true that occasionally

TABLE II

CAUSES OF DEATH DURING FIRST FOURTEEN DAYS (HOLT AND BABBITT)2

		ER 1	t	ER 7 YB	i .	o 14 Ays	1	L IN DAYS	
CAUSE OF DEATH	PRE MA TURE	FULL TERM	PRE MA TURE	FULL TERM	PRE MA TURE	FULL TERM	PRE MA TURE	FULL TERM	GRAND
Congenital Weakness	93	2	120	7	14	$\frac{}{2}$	134	9	143
Accidents of Labor	1	14	1	32			1	32	33
Pneumonia			3	9	3	13	6	22	28
Atelectasis	3	7	3	14	1	7	4	21	25
Congenital Syphilis	5	0	6	1	6	0	12	1	13
Malformation		4	2	7	0	3	2	10	12
Hemorrhage				8		2		10	10
Sepsis				2		7		9	9
Asphyxia		7		8				8	8
Accidental		1		2				2	2
Undetermined		3		8				8	8
Total	102	38	135	98	24	34	159	132	291

a skin infection of the nature of pemphigus neonatorum will be fatal since as yet, we have not learned how to prevent the occurrence of this condition. Taken by and large this group of cases should be eliminated from the list of fatalities of this age.

In regard to the children with diseases peculiar to the newborn, we are in a distinctly bad position. On the other hand, while we do not know the cause of hemorrhagic disease of the newborn, we do know a method of treatment—blood transfusion—which in the vast majority of cases will produce a cure if given at the pioper time. Of the children with severe forms of interiors of an infectious nature as yet our knowledge is incomplete. It has been hinted that this condition is due to a disturbance of the hematopoietic organs and that splenectomy may be of value. This remains for future study. The other conditions are rare

Holt and Babbitt,2 Table II, have recorded the cause of death of 291 infants in the first fourteen days of life. If we arrange these ac-

cording to the four groups we find from the accompanying table that in the first group we may include

Congenital weakness	143	саве
Atelectasis	25	case
Malformations	19	CORP

making a total of 180 cases or over 60 per cent of the total. In the second group are those due to trauma. We may include accidents of labor or 33 cases. This leaves 78 in which in 8 the cause was undetermined leaving 70 to be divided between the other two groups. Of these the following may be classed in the group of infections—

Congenital syphilis	13
Bepuls .	ð
Preumonia	28

making a total of 50 For the diseases occurring in the first few days of life, the following may be included—

Hemorrhage Asphyxia Accidental deaths	10 8 2
	_
	20

In my experience the figure for pneumonia is quite high but the general statement holds true here as in our estimate

In the first group it is difficult to see how any could have been saved. Perhaps under ideal circumstances a few of the cases of congenital weakness might have been but when we consider that these children were all born in the hospital we may be sure that every means was used to save them that the most intelligent supervision could devise. It is true that these statistics are somewhat old having been brought out in 1915, but conditions, I am sorry to say, have not materially changed since that time. As to the accidents of labor, or trauma, the figure is very low. Thirty three or less than 10 per cent, is a much lower figure than is given in most reports as the percentage of deaths from mouries.

Adair in his statistics of deaths of full term children gives a per centage of 39 7 as due to birth trauma and of those children which were viable at the beginning of labor, a death rate of 41 8 per cent. It should be noted that the statistics of Adair were of general obstetrical practice, largely outside the hospital, and they did not represent obstetrics carried on by experts. Certainly this figure of Holt and Babbitt would represent the absolute minimum of deaths from injury.

As to the third group sepsis pneumonia and congenital syphilis, these should be prevented, and under our present regime the last cer tainly would be taken care of to a large extent. We would expect to do away entirely with deaths from congenital syphilis with proper prenatal care. The third group represents conditions which are very

TABLE III

	1001	1090	1000	1001	1995	1996	1097	1098	1999	1930	1931	1939	Total	
	1701	1	212	270	750	707	100	200	GTR	796	07.1	1480	0064	
No of Cases	) (a)	0# <i>)</i>	720	71 65		ē 61	170 750	- c1	2 -	3 -	1 -	2027	21	0 205%
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Canso of Death			Pneun	Pneum	Labor		Pur	Labor			and			
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Birtha*	760	745	627	772	753	787	821	827	949	736	986	1501	9991	
Stillbirth	17	19	14		21	20	19	18	13	14	17	25	550	2 26%
CAUSES														
Macorated	9	9	က	17	10	11	G	10	9	∞	ō	c	100	
Promaturity	9	<del>-1</del> 1		-1	က	~	<del>-1</del>	က	<b>⊢</b> ₁	<b>C</b> 3		4	33	13 %
Agnivan	က	ø	<u>-</u>	6	œ	9	ıo	ō	9	4	9	7	74	
Concental Defects	C1	Н	ಣ	C.J	0	0	0	0			4	Н	13	
Congenital Syphilis							Н						<b>c</b> 7	•
Pulmonary Atelectasus												က	ಣ	
Intracranial Hemorrhage												Н	_	
Neonatal Deaths	15	13	G	14	12	18	15	23	11	ø0	10	15	166	166%
CAUSES														
Prematurity	က	ıc	c	ນ	ıΩ	œ	6	14	9	co	က	4	72	
Asphytan	က	Ċ.J		က		က	Н	9					18	
Intracranial Hemorrhage	-	<b>c</b> 3	⊣	<b>c</b> 1	c)	က	က	Н	H		<b>C1</b>	63	50	
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Congenital Defects	ro			Ç1	4	,	01		က	က	٦	9	28	
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Sepsis									П					% 9 0
Syphilis					ന	-		-			<b>c</b> 1		7	
Other Causes		24	Ţ.			ı						ĭ	9	30 %
Not accurate for 1921 to	to 1930 i	1930 inclusive												

a. Apnea and nephritis.
b. Deby dration.
d Air embolism in coronary artery

hard to deal with Of these, hemorrhage in the newborn will respond to treatment as a rule, but it is altogether likely that this croup of ten cases could not even under ideal conditions be better than halved Deaths from asphyxia under the conditions of these cases will prob ably not be reduced. Accidental deaths of course are things which may be guarded against, but in the nature of things there will always be a few and this number of less than 0.5 per cent we can scarcely expect to reduce. If we again sum up the situation so far we find that in Group I of 180 cases, we probably would not be able to save more than 30 at the outside Croup II-33-we could probably not reduce Group III-50-the figure for sensis could probably not be reduced, but that for concentral syphilis could be almost entirely erased Pacumonia might be slightly reduced leaving perhaps thirty cases in this group which we could not expect to save Group IV-20 -we might be able to reduce by five Of the 291 cases 8 were un determined leaving a total of 283 to be reckoned with Thus by our present count under ideal conditions, we could not expect to save more than 55 or about 18 per cent

I should like at this point to introduce a table (Table III) of the results obtained in the Presbyterian Hospital obstetric out patient department (Chicago) in the years 1921 to 1932 inclusive. This is an out patient department conducted for teaching at Rush Medical Col lege, the labors being attended by students. All normal labors are taken care of in the home, pathologic ones so far as possible are taken to the Presbyterian Hospital We see from this table that the num ber of stillbirths exceeded that of neonatal deaths by 60 The out standing difference between the causes of death in this series and that of Gillespie is that in this series nearly the entire group can be classified as due to inherited causes of one kind or another Only 2 cases of congenital syphilis and one of intracranial hemorrhage out of 226 would not fall in this category I might say that practically all of these diagnoses were made at autopsy so that there was very little guess work as to the cause of death As to the neonatal deaths they conform very closely to those of Holt and Babbitt, so that we will not discuss these further at this time

Let us now consider the question of intracranial hemorrhage as a cause of death at this period of existence. If we compare the statis ties of Holt and Babbitt with those of Adair, we find in the former that in full term children accidents of labor account for 32 or approximately 10 per cent (Presbyterian Hospital 20 or 12 per cent), while in the statistics of Adair the figure is 31 per cent. This difference of 21 per cent is a very great difference. Three times as many infants born under the conditions which were represented in Adair's report died as compared with the infants born in the Sloane Maternity Hospital of New York City and the Presbyterian out patient service in

Chicago To evaluate this discrepancy is very hard. At first glance, it would seem that this difference was due to a difference in the type of obstetries employed in the two situations. On the other hand, while we must admit that there is probably some reason for this conclusion, or rather that it in part accounts for the difference, we must remember that there is a vast amount of racial difference between the populations of New York and Chicago and the population of Minnesota. Whether or not this plays a part in these statistics, it is impossible to say, but there can be very little doubt but that good obstetries did play a part.

It is impossible to tell from the statistics of Gillespie what proportion of the deaths from birth trauma was the result of interference with birth, and how much was the result of the natural processes of labor. For the consideration of our subject, this is the important point. If the processes of labor are responsible for intracranial hemorrhage of the newborn (which accounts for the vast majority of fatal birth trauma), then our efforts to reduce the mortality from this cause are likely to be largely futile. If, on the other hand, the cause of intracranial hemorrhage is to be carried back in the majority of instances to obstetric interference, it will be possible for us to attack this problem with some prospect of success.

A more careful analysis of the causes of fetal deaths brings out the fact that most of them are to be accounted for on the basis of prematurity and that a large proportion of these cases born in the normal process of labor cannot be attributed to interference by the phy-It is also true that in full-term infants born by Cesarean section or precipitate labor it is not unusual to have intracranial hemorrhage, and even in the normal process of labor, children with large heads may occasionally be victims of the same condition has been my impression in the study of this subject that while we may be able to reduce this group materially by less interference at the time of labor, there still would be a very large proportion of cases where this will not be possible Among these may be grouped the cases of intracranial hemorrhage which occur in spontaneous labors, Cesarean sections, and precipitate labors Again we must expect that if we delay the interference too long in many cases there is likely to be hemorrhage simply from the exaggerated efforts of the uterine musculature Like so many things in medicine, the ultimate result depends not upon dogmatic rules but upon judgment, and we cannot expect to have perfect judgment exercised in every case of labor If we are able, therefore, to reduce the number of cases of intracranial hemorrhage in the newborn by one-third, it would seem to me that that would be as much as we could expect

#### SUMMARY

When we sum up this estimate as to the prospects of saving the newly born infant and the child not yet born, we find that the pros picts are not so bright as we could wish. Statistics of other countries are misleading because of different methods of compilation, and we are only interested in them in an academic way. What we wish to know is what chances have we of reducing this mortality under present and future conditions. Under present conditions our chief hope hes in the reduction of the cases of deaths from congenital syphilis reduction of cases of sepsis and of birth trauma. The large group of cases of malformation congenital debility and allied conditions offer very little hope. We must not be carried away with en thusiasm to the point where we may expect a result comparable to that which has been brought about in the reduction of infant mor tality in general. This is the most remarkable life saying activity that has taken place at any time since the introduction of smallpox vaccination. The problem was much more clear and the chances of success much greater when this effort was started than is true at the present time with respect to the fetus and the newly born. But the position is not quite so dark as these statements would seem to indi-Medical science is advancing rapidly and we as yet have accomplished little or nothing in the study of these conditions closer study may develop some very unexpected leads It is not im possible that we may find that nutrition does play a part in congenital We may be able to grasp the causes of some of the fatal conditions in the newly born infant and it may be that with a better understanding of engenies we will be able to prevent some of the congenital malformations and conditions which at the present time have proved so fatal This program, however, is not a program of months but of years and probably of decades, and those who interest them selves in this life saving venture must realize the problems ahead of them and the chances for success

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# RENAL CHANGES IN THE RABBIT RESULTING FROM INTRA-VENOUS INJECTION OF HYPERTONIC SOLUTION OF SUCROSE

# HENRY F HELMHOLZ, M D ROCHESTER, MINNESOTA

In A SERIES of experiments on rabbits in which hypertonic solution of sucrose was used to produce maximal diuresis, marked cytologic changes were observed in the convoluted tubules of animals that were killed twenty-four hours after injection. It seemed worth while to determine the mode of development of these cytologic changes, and to attempt to correlate them with the possible functional changes of the kidneys. If, in spite of the histologic changes, the functional changes were minimal, the diuretic action of intravenously injected sucrose might prove safe as well as useful therapeutically

Various observers<sup>2</sup> have recorded changes in the epithelium after injection of hypertonic solutions of sugar. But more detailed studies of the histologic changes, or the effects of repeated injections on the renal epithelium have not been given

## DEVELOPMENT OF LESIONS AFTER A SINGLE INJECTION

Animals were given injections of large amount of 20 per cent sucrose for one hour. After intervals varying from one hour to fifteen days (one, three, six, twelve, twenty-four, forty-eight, ninety-six, one hundred twenty, one hundred sixty-eight, two hundred forty and three hundred sixty hours) the animals were killed and the changes in the renal structure noted (Table I)

The swelling of the convoluted tubules began after one hour and reached its maximum at forty-eight hours, so that not only the cells, but the tubules themselves seemed larger than normal. This enlargement of the cells persisted for about a week and then gradually subsided, so that at the end of fifteen days the cells appeared normal. In the early stages, the vacuolar degeneration was marked, it was of maximal intensity in the tubules of the ascending limb of the loop of Henle. In some sections a definite zone in the cortex adjacent to the medulla was formed by this change in the epithelium. After one hour the tufted edge of the epithelium was still present, but it was absent after three hours. After twenty-four hours, the protoplasm became finely granular and small in amount, so that the cells came to stain lightly, and after forty-eight hours, the appearance of the cells was that of clear cells of hypernephroma. After twenty-four to forty

eight hours, the cells of the tubules were so swollen that the lumen was almost obliterated (Fig. 1). When a lumen was present it was filled with finely granular material which stained pink in sections prepared with hematoxvin and cosin. After one hour the nuclei were round or oval, after three hours they appeared shrunken, and in five of six specimens obtained in the first forty eight hours the nuclei of the tubule cells were definitely shrunken, and cellular outlines were rather indistinct. This nuclear change was not noted after the second day. After the seventh day the swelling of the tubular epithelium began to tubside. Ten days after injection, some enlargement of the tubular epithelial cells was still present and the protoplasm was still finely granular and family staining. In specimens obtained at the

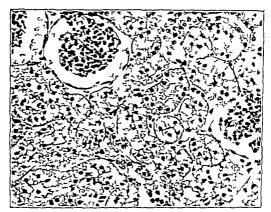


Fig. 1 -1 scuolar degeneration and swelling after twenty four hours.

fifteenth day the kidney was normal. When smaller doses of sucrose were given, the tubules were practically normal after one week.

In specimens obtained at one, three and six hours, there was no ma terial within Bowman's capsule. In these early stages an excess num her of cosinophilic leucocytes in the glomerular capillaries were seen these were absent later. The glomerular tufts did not fill the capsule. After twelve hours there was less space between tuft and capsule, and in many cases, the space was filled with cosin staining granular material. The specimens obtained at twenty four and forty-eight hours resembled those obtained at twelve hours. After ninety-six hours, the glomeruli appeared normal.

It should be noted that the diuresis which reached its maximum in the case of an animal that excreted 150 cc for each kilogram of body weight each hour, was sufficiently great to produce a moderate degree of hydronephrosis The hydronephrosis was seen in animals killed immediately after injection

The changes produced by injection of 50 per cent solution of sucrose resembled closely those produced by 20 per cent solution, except that at the one- and three-hour stages, the epithelium seemed lower than normal, retained its tufted edge, and the vacuolar degeneration was less

Injection of 10 per cent sucrose produced decidedly less renal injury in the convoluted tubules, the ascending limb of the loop of Henle seemed most involved, but at no stage was tubular swelling so intense, nor was the lumen at any stage completely obliterated

TABLE I

RENAL CHANGES AT VARYING INTERVALS AFTER INTRAVENOUS INJECTION OF SOLUTION OF SUCROSE

RABBIT	HOURS AFTER IN JECTION	URINE, C C PER KG PER HOUR	SWELLING OF TUBULAR EPITHE LIUM	VACUOLAR DEGEN ERATION	DETRITUS IN LUMEN	GRANULAR DETRITUS IN GLOMERULAR SPACE	SHRUNK EN NUCLEI
1	1	190	+	++	++	_	_
2	3	185	+	++	++	_	++
3	6	23	+++	+++	++	+	+
4	12	143	+++	+++	+	+	_
5	24	83	++++	++++	+	++	-
6	48	60	++++	++++	_	++	_
7	96	93	+++	++	+	_	++
8	120	40	+++	++	-	+	+++
9	168	153	+++	++	_	- 1	_
10	240	75	++	+ 1	-	- 1	-
11	360	117	+ 1	+		-	_

### DEVELOPMENT OF LESIONS AFTER REPEATED INJECTIONS

Series 1 —It was evident that single injections of sucrose would be tolerated by the rabbit's kidney without permanent injury, and that the appearance of the tissues would return to normal in from seven repeated injections, at intervals less than those necessary for complete repair, would injure the convoluted tubules and affect the functional capacities of the kidney The first eighteen animals were given injections at intervals of from five to seven days and were given from three to eight injections The amount of 20 per cent solution of sucrose injected varied from 542 cc given in eight injections to a rabbit weighing 15 kg to 1,480 cc given in four injections to a rabbit weighing 36 kg. The younger rabbits did not tolerate the injec-In the kidneys of animals killed tions as well as the older animals within five days after the last injection, there were only the typical changes described as following the single injections in forty-eight hours, but the changes varied considerably in their intensity

Series 2- othing of note was observed in the first series of animals Therefore, it was decided to increase the number of injections, and a second series of animals received from ten to twenty two injections at intervals averaging about seven days. In Table II the details of weight, number of injections, total amount of 20 per cent solution of sucrose, intervals between injections interval between last injection and death of animal and the histologic findings are given clearly evident that even after numerous injections the epithelium dis closed a remarkable power to return to normal. This was most evident in animals 1 and 2 which died eight days after the twelfth and tenth micetions, respectively, and in the kidneys of which there were practically no histologic changes. This recuperative power was exhibited to a slightly less degree in animal 8 which died eleven days after its fourteenth injection, and in which there were only slight changes in the renal tubules In rabbits 5 9 and 10, which died two or three days after the last injection, the changes in the convoluted tubules were striking. The cortex of the kidney resembled hypernephroma with compressed glomeruli. With the exception of rabbits 6 and 7, rabbit 9 received the largest amount of sucrose 1800 cc in sixteen injections, but there were no changes that in any way differed from those found in a rabbit that had been killed forty-eight hours after a single large injection In its sixteenth injection it received 150 e.c. of 20 per cent solution of sucrose in fifty minutes and during that time put out 200 cc of urme. Ten days before its death, and forty-eight hours after the fourteenth injection, the output of phenolaulphouphthalein was 60 per cent

Rabbit 4 was of interest on account of rather peculiar changes seen at necrops, after only fifteen injections. The entire convoluted tubule took an excessive amount of stain, and although the animal died on the day of injection, the cells of the tubules were not typically swollen. The nuclei were dense and deeply stained. The picture was different from that seen in any of the other animals. In the three animals which received sixteen, twenty one, and twenty two injections, such changes were not seen, therefore the picture presented probably was not the result of repeated injection of sucrose

Rabbits 8 and 9 received fourteen and sixteen injections, respectively, and the changes varied with the interval of time after the last injection. The changes were mild in animal 8 which died eleven days after the final injection and marked in animal 9 which died three days after the final injection.

Rabbits 6 and 7 received the largest number of injections, rabbit 6 received 3 025 c.c. in twenty-one injections and rabbit 7 2 555 c.c. in twenty two injections. In order to show the amount of sucrose in jected the figures are given in Table III there also are given the time of removal of the right kidney and of determinations of blood urea

RENAL CHANGES AFTER REPEATED INJECTION OF 20 PER CENT SOLUTION OF SUCROSE

		СОММЕНТ	After 12 injections, blood urea 22 mg in each 100 cc, excretion of phenol	After 10 injections blood uren 8 mg in	phonphthalen, 75 per cent, vacuolar decembers on increase.	age of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of	Specimen removed for control before in	jection, negative Specimen removed for control before in	Jection, negative Specimen removed for control, negative,	blood urea 116 mg in each 100 cc, excretion of phenolsulphonphthalem, 5	per cent Marked compression, atrophy of ascend	ing limb of loop		
		ROSIB	0	0		0	++	+	+	_	+	¢	0	0
		META SCLE PLASIA ROSIS	0	0		0	++++	0	0		0	0	0	0
ES		ATROPHY PLASIA	0	0	·	0	+	0	++		++++	+	0	+
THRITAR CHANGES		DEGEN ERATION	0	0		0	++	0	+ + +		+++	+	+++	+++
TUBLL	SWELLING	CONVO- LUTED	0	0		+++	0	+ + + +	++++	•	+ + +	+	++++	++++
	SWEI	ASOEND ING LIMB OF LOOP OF	+++	0		+++	0	+ + + +	++		-+ -+ -+	+	+++++	+++++
	DAYS BF	TWEEN LAST INJECTION OF SOLUTION OF SUCROSE AND DEATH	s	80		9	0	63	Н		61	11	က	8
		SOLUTION OF SUCROSE INJECTED, TOTAL C C	1,542	720		965	1,036	1,271	3,025		2,555	1,482	1,800	1,161
	INJEC	TIONS OF SO- LUTION OF	12	10		10	15	13	21		61 61	14	16	=
		<b>ТКІВНТ,</b> КВ	2.5	16		2.4	2 75	2 71	7 6		3.2	2 0	23 73	2.75
		RABBIT	-	61		က	4	10	9		7	ø	0	10

and of exerction of phenolsulphonphthalein. After nine and ten in jections the output of phenolsulphonphthalein was 80 and 70 per cent. A week after right nephrectomy, and following the thirteenth injection in rabbit 6, and the sixteenth injection in rabbit 7 the output of phenolsulphonphthalein was respectively 60 and 55 per cent. At no time after removal of one kidney did the animals exercte a volume of urine greater than the volume of sucrose injected. The general condition of the animals became poor and they lost weight.

Animal 6 weighed 3 1 kg at the beginning of the injections one hun dred eights two days later, twents four hours before it died, it weighed only 21 kg. At the time of the last injection it seemed very weak and put out only 10 cc of urme while 85 cc of sucrose was injected The day following this injection the value for blood urea was 116 mg for each 100 cc, and the output of phenolsulphonphthalem was only 5 per cent in two hours. The animal was so sick that it was feared it would not live another day, therefore it was killed. Postmortem ex amination disclosed that the animal was markedly emaciated left kidney was practically normal in appearance in spite of the fact that a piece of it had been removed after the tenth injection removal of the specimen had resulted, of course, in a small scar was slightly increased in size, and was light brown The surface was slightly irregular. The ureter and bladder were normal tion of the other organs disclosed nothing abnormal Three specimens were available for microscopic studies. The first was derived from the piece of the left kidney that had been removed six days after the tenth The vacuolar degeneration of the cells of the ascending limb of the loop of Henle was marked, as was also that of cells from some parts of the convoluted tubules Some of the convoluted tubules had undergone little change, in others the cells appeared markedly swol len and the outlines of the cells were indistinct. Some focal nephritis was present. The second section, removed from the right kidney, six days after the thirteenth injection, differed very little from the first section. The degeneration and swelling of the cells of the ascending limbs of the loops of Henle were more marked that of the cells of the con voluted tubules, however, were, if anything, a little less marked and many tubules appeared normal. Some focal nephritis was present. In the third section taken at necropsy from the left kidney after twenty one injections there was much more focal nephritis than there was in the other two sections The protoplasm of the cells of the convoluted tubules was finely granular and the cells were swollen so as to oc clude the lumens of a few of the tubules Most of the cells of the tubules were swollen relatively little The cells of the ascending limb of the loop of Henle contained even less protoplasm, in some places the cells were greatly swollen but in others they were atrophic. The structure of the kidney otherwise was normal, and the changes, other

than the focal nephritis, were not nearly so intense as in the kidneys of many of the other animals which received fewer injections. Mallory-Heidenham stain did not disclose any diffuse increase of connec-

TABLE III

RESULTS IN EXPERIMENTS IN WHICH LARGEST NUMBER OF INJECTIONS OF SOLUTION OF SUCROSE WAS GIVEN

INJECTION	SOL HERE	N OF SU	
OF	CROSE		COMMENT
SOLUTION			CONDIENT
OF SUCROSE	RABBIT 6*	RABBIT 7 f	
1	180	125	
$\bar{2}$	200	115	
3	50	115	
	100	150	
5	200	100	
4 5 6 7	200	150	
7	100	150	
8	150	100	
9	45	165	Rabbit 6 after ninth injection excretion of
-			phenolsulphonphthalem 80 per cent
10	150	150	Rabbit 6 small piece left kidney removed
			Rabbit 7 after tenth injection, excretion of phe
į			nolsulphonphthalein 70 per cent
11	95	50	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
12	150	200	
13	200	25	Rabbit 6 right kidney removed 133 days after
	ĺ		first injection, 7 days later blood urea 24 mg in each 100 cc and excretion of phe
			mg in each 100 cc and excretion of the
Ï	)		nolsulphonphthalein 60 per cent
14	200	40	
15	150	50	
16	50	200	Rabbit 7 right kidney removed 138 days after
			first injection, 7 days later blood urea 27
1			mg in each 100 cc. and excretion of phenol
ļ	į		sulphonphthalem 65 per cent
17	200	175	·
18	200	100	
19	40	45	
20	180	200	
21	85	100	Rabbit 6 on day after twenty first injection,
ł	1	l	blood urea 116 mg and excretion of phenol
	1	1	sulphonphthalem 5 per cent, animal very
Į	· ·	İ	weak so killed 182 days after first injection
22		50	Rabbit 7 second day after twenty second injec
	ì	ļ	tion found dead, 176 days after first injection
I		}	(animal pregnant)
Total	2,925	2,555	

\*Rabbit 6 weight 3 4 kg Urine negative on culture and microscopically †Rabbit 7 weight 3 2 kg Urine negative on culture and microscopically blood urea 7 5 mg in each 100 c.c and excretion of phenolsulphonphthalein 100 per cent.

tive tissue Microscopic changes that would account for the high value for unea, and for the final low value for excretion of phenol-sulphonphthalein were not found

Animal 7 died twenty-four hours after the twenty-second injection It appeared to be in good condition following the last injection of 50 e.e. of sucrose, but was found dead the following morning, one hundred seventy-six days after the first injection. There was considerable

postmortem change The right kidney was definitely enlarged and the tissue was opique and grayish. On section, the cortex was definitely increased in width. The pelvis and ureter were normal. The other abdominal organs were normal. There were available for histo logic study, sections from the left kidney, that had been removed after sixteen injections, and sections from the right kidney, made at necropsy. The sections from the left kidney disclosed relatively little enlange. The cells of the ascending limb of the loop of Henle and those of the convoluted tubules, disclosed some vacuolar degeneration but relatively little swelling. The interval of six days seemed to have been sufficient to allow the cells to return to normal size. There was some chronic focal nephritis. The section taken at necropsy, twenty

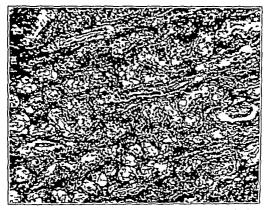


Fig 2 - Epithelial atrophy and scierosis after twenty-two injections.

four hours after the twenty second injection, disclosed marked changes that in part might have taken place postmortem. There was marked degeneration and swelling of the tubules and the cells especially those of the ascending limbs of the loops of Henle, appeared crowded together as if undergoing strophy (Fig 2). The line between the cortex and medulla was difficult to discern. There was considerable diffuse increase in connective tissue especially in the lower portion of the cortex and upper part of the medulla. Sections stained with Mallory Heidenhain stain disclosed the increase in connective tissue definitely this was especially evident when compared with a section from rabbit 6 stained in the same way, in which no such increase in connective tissue was seen. It is to be regretted that this animal was not found immediately after death, for it is the one animal in which

atrophy of the tubules and diffuse increase in connective tissue occurred. It does not seem likely that postmortem changes can account for this difference, for the cellular outlines were well preserved. These changes, which were absent in rabbit 6, may represent the more severe tubular changes that follow injection continued over even longer periods.

Series 3—A third group of seven animals received a smaller number of injections of solution of sucrose, but at shorter intervals. Animals 1 and 2 received their injections at intervals of two days, the former received six injections, and the latter, eight. The other five animals received four injections, at intervals of three days. In all the animals in which tissue was available for histologic study the renal



Fig 3 -Tubular degeneration after eight injections at two-day intervals

changes were marked, except in animal 6 which was not killed until eight days after the fourth injection. The kidneys of all but the first two animals had been removed one week before the first injection. The changes found in this series of experiments were the most uniformly marked, and represented the changes resulting from injury that was repeated before the process of healing could return the cell to normal. Fig. 3, picturing tissue of animal 2 after eight injections at intervals of two days, presents the most marked acute lesion that I have encountered. The swelling of the tubular epithelium was most marked and the lumen of most of the tubules was closed. Fig. 4 illustrates the changes after four injections at intervals of three days. It represents changes almost as intense, and some calcareous deposits probably not related to the injections.

The most striking feature of this series of experiments, aside from the changes seen, was the marked reduction in output of phenolsul phonphthalein in the five experiments in which determinations were made. In two of the experiments the urine was taken for only two hours after injection of the phenolsulphonphthalein in the other three for four hours (Table IV). The output in the five experiments was extremely low 5 per eent in three eases 3 per eent in one case, and zero in the fifth ease. The output of phenolsulphonphthalein by animal 6 had risen to 15 per eent on the seventh day after the last injection, by animal 7 it was 20 per cent seven days after the last injection, and 80 per eent thirteen days after the last injection

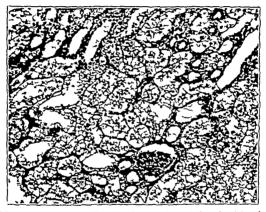


Fig. 4-Tubular degeneration after four injections at three-day intervals.

The typical picture twenty four to forty-eight hours after a large injection of 20 per cent solution of sucrose was that of hypernephroma. The entire system of tubules of the cortex lost the solid pink color as seen in a section stained with hematoxylin and cosm and consisted of clear cells, with a small amount of pink granular material. The cells were so swollen that there appeared to be only a very narrow lumen or no lumen. After six to fifteen days, depending on the dose, the epithelium again appeared normal. A second injection would produce the tame histologic appearance, and if continued for as many as twenty two injections, provided the interval of time was seven days or more, resultant changes would not affect the excretory functions of the kidney. If the interval of time was only three days, definite functional changes resulted, as measured by the output of phenolaulphon phthalein.

TABLE IV

RESULTS IN EXPERIMENTS IN WHICH A RELATIVELY SHALL NUMBER OF INTERTIONS OF SOLUTION OF SUCROSE WAS GIVEN, BUT AT RELATIVELY SHORLIS

COMMENT					Pyelitis, shriinken nuclei							Postmorton chance marked	name of many control of		
DAYS BE TWEEN LAST INJECTION OF SOLUTION OF SUGROSE AND DEATH				¢1							က				9
VACUOLAR DEGEN FRATION				++							+++		•		
SW ELLING OF TUBULES				++++							++++				***
OUTPUT OF PHENOL- SULPHON PHTHAL FIN, PER CENT											3+				ıç
INTERVAL BE TWEEN INJEC TION OF SUCROSE AND OF PHFNOL SUI PHON PHTHALEIN*										ı	5 hours				l day
SOLUTION OF SUGROSE,	80 100	104	105 82	100	100	85	103	100	100	70	93	100	83	T00	100
WPIGHT, JECTION OF SOLUTION OF OF SU CROSE, MG	11 7 11 9	11 13	11 15	11 19		11 9	11 13	11 17	11 19	11 21		1 20	 	72.7	1 30
менант, ка	2 55				2.5					-		35			
RABUT	1				C1							<del>;</del>			

£NJKKOO	Died at end of experiment		Deposit of enleium in tubules			Output of phenolaulphonphthalein	seventh day to per cent chronic	5	Output of phenoleulphonphthalein	seronth day 20 per cent thir-	teenth day 80 per cent no see	tions; animal lived
DAYR BE TWEEN LART INJECTION OF ROLUTION OF HUCKOSF AND DEVITE		e			12			or				
VACUOLAR DEGEN FRATION		+++			++			+++				_
RIVELLING PACUOLINE OF PEATION		+++			++++			+				
OUTPUT OF PIENOI- SCLPHON PHYNAL- EN					+			3				<u> </u>
INTERVIL HE TOY OF TION OF BUCROSE AND OF PITENOL- SULPHON PHITHLEIM					1 day			1 day				1 day
BOLUTION OF SUCROSE,	105	ß	35	28	100	100	8 5	100	100	300	199	2
DATE OF IN JECTION OF BOLUTION OF BU CROSE, MG.	12 31 1 3	1 9	1, 31	9	1 9	1 00		130	1 33	63	86	130
WELGHT	2.75		6.6			11.2			273			
KABBIT	#		ţţ			‡9			7.1			

Phenouniphopphinish, is ampule, given in 50 cc. Ringer's solution intravenously withe collect of for 1 hours (Urine collected for 1 hours, and 1 for 1 hours that kithney removed 1 week before indections of solution of sucrose were begun.

## CHANGES IN THE KIDNEYS OF HUMAN BEINGS

Changes similar to those described occurred in the kidneys of human beings after injections of hypertonic solution of sucrose. If, as a result of repeated injections of solution of sucrose for the purpose of inducing diuresis, permanent injury would result, a contraindication to use of this solution as a diuretic would be evident. Fig. 5 illustrates the condition of the kidney of the human being forty-eight hours after a series of injections of solution of sucrose

The course of the illness was as follows A boy aged eight years was brought to the clinic When he was three months of age, a diagnosis of congenital syphilis was made and treatment had been continued since that time The illness for which treatment was sought

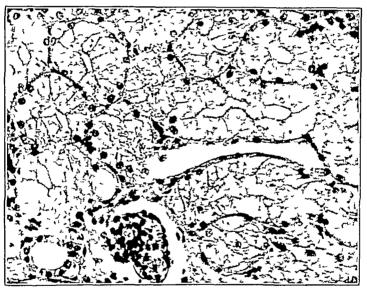


Fig 5 -Kidney of a patient after three injections

at the clinic was meningitis. The spinal fluid contained diplopneumococci, type 4, on culture. The boy's condition rapidly became worse, high fever developed, and death occurred on the fifth day after his admission. On the second day after admission he was given 1,000 c c of 20 per cent solution of glucose intravenously, on the third day, he was given 450 c c, and on the fourth day, 790 c c. This was administered after sodium amytal had been given hypodermically

At necropsy there was evidence of acute meningitis and of congential syphilis. The epithelium of the ascending limb of the loop of Henle, and of the convoluted tubules, was swollen and pale, the cells were represented by a thin membrane, and a very pale, faded cytoplasm. The swelling of the epithelial cells was so marked as completely to obliterate the lumen of the tubules. There was considerable pink granular material within Bowman's capsule.

#### COMMENT

As the result of the experiments in series 3, it seemed evident that injections at intervals of three days seriously lowered the function of the renal epithelium as measured by the output of phenolsulphon Intervals of three days between injections it seemed were insufficient to permit return of function of the renal tubules

The changes produced in the epithelium of the ascending limb of the loop Henle and convoluted tubules were striking, and so different from those previously described for the tubular system, that some speculation as to mode of origin of these changes seems justified.

Marshall has shown that the aglomerular fishes do not secrete for eign sugar, therefore, it would seem probable that sucrose is excreted by the glomeruli, and that it is passed from there through the tubular system into the renal pelvis. The epithelium which normally concentrates the urmary constituents by the absorption of water is, in all probability doing the same thing during diuresis induced by sucrose The tremendous outpouring of urine, which may reach 150 cc for each kilogram of body weight, each hour, involves a huge functional load on the kidney, which is manifested only by the tubular changes Apparently the glomerulus is in no way injured by putting out this large amount of urine, even though repeated injections are made at a time when the renal tubules are swollen The changes in the con voluted tubules can be thought of as a physiologic response to a maxi mal effort in retaining water for the body or perhaps, as a response to a physical injury from overwork. The return of normal in a rela tively short time indicates the absence of severe, irreparable injury The lesions resembled those Hartman produced in the kidney when he transplanted the lower ends of the wreter high into the duodenum and thus established a closed circuit for excretory waste products

#### SUMMARY AND CONCLUSIONS

It is evident from these experiments that repeated injections of hypertonic solutions of sucrose do not do any harm to the tubular ap paratus or glomeruli of the kidney unless injections are given re peatedly at short intervals

Four injections of hypertonic solutions of sucrose at intervals of three days reduce the output of phenolsulphonphthalem materially with a return to normal output after two weeks

It may be concluded that intravenous injections of hypertonic solu tions of sucrose, for the purpose of diuresis or of dehydration, given singly or repeated after intervals of five to seven days, will not prove harmful.

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# FAMILIAL RETARDATION IN OSSIFICATION OF THE CARPAL CENTERS

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THE instance of familial retardation in the development of carpal centers to which we wish to call attention is interesting in itself from several points of view, but has greater significance in connection with the rôle of constitutional and of local factors in the ossification of eartilage. The case involved two brothers whose clinical course we were able to follow, year by year, for a period of over five years and until the defect in ossification was completely corrected. During this observational period it was possible to make careful measurements of the various parts of the body, to carry out chemical examinations of the blood and to observe the physical and mental progress of the boys.

CASE 1—L Y (older brother), a Jewish boy, was born at full term, February 21, 1921. His mother, an Austrian, twenty nine years of age, physically normal, had been married two years before he was born. There had been no miscarriages About two years later she had another child whose history is given below. A third pregnancy terminated, however, at the eighth month, when she gave birth to an anencephalic monster weighing 2 pounds, 7 ounces. The father, also of Austrian extraction, was about 37 years of age and physically sound. There was no history of familial disease.

Throughout the first pregnancy the mother enjoyed fair health, her diet ap parently was adequate. The delivery was normal, the respirations of the infant spontaneous and there were no convulsions. Birth weight was 7 pounds, 4 ounces. The infant was breast fed until about 14 months of age. During this period attempts were made to add other articles of food to the diet, but without suc.

 $\begin{tabular}{ll} Table I \\ Data in Regard to Development of the Older Brothep ($L$\,) \\ \end{tabular}$ 

		AGE	WEIGHT	неіснт	COMPARISON WITH		BEE OF CENTERS
FIGURE	DATE	(YEARS)	(POUNDS)	(INCHES)	BALDWIN WOOD STANDARDS	rouis	PRYOR'S STANDARD (MALE)
					per cent		
-	3/15/27	6	421/4	44	-4	2	6 - 7
2 a	12/ 5/27	63/4		i '		2	8 - 7
	5/ 5/28	71/6	49¾	461/4	+1	2	6 - 7
2 Ъ	1/13/29	8	4911/16	4914	-11	2*	6 - 7
2 c	11/25/29	83/4	551/16	491/4	2	5 & 6	7
	10/12/31	11	63	53	-6	l	1 8

Right ulna distal epiphysis appears 2 years retarded

cess. Cod liver oil was never given. After the fourteenth month thin cereals awichael, broth and potatoes were taken by the child who still refused fresh fruits and ment. Motor development was retarded. The infant was able to support its head at 6 months of age and sat up at 0 months. He never crawled and was able to walk with support only at 17 months and walked alone by about 18 months. Talking also was delayed, single words being spoken at 18 months and he was unable to put two or more words into a phrase until 2 years of age. The first tooth crupted at 10 months.

Up to about 6 vents of age, the child had no illnesses of importance Tonsillectomy and adenoidectomy were performed at 2½ years. At 6 years, how ever, he was admitted to a he pital for acute mastelilitis which became complicated by an acute suppurative arthrits of the right knee joint. The knee was incised and drained, leading to ankylosis of the joint. The clinical course of the disease was stormy and convalence protracted.

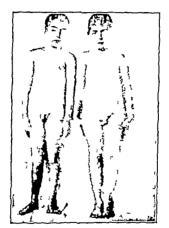


Fig 1.-L. Y. eight years nine months, and G Y., seven years.

Upon recovery, physical examination showed a poorly nourished boy weighing 42 pounds, 4 ounces, with a height of 44 inches. The circumference of his head was 1814 inches, that of his chest 22 and of his abdomen 1014 inches. The mid point of the body was at the symplyris publs. His general expression was dull and his color poor. He was a mouth breather. The musculature was flabby and the subcutaneous fat deficient. The posture was poor due to the deformity of the right lower extremity. The spine showed a compensatory scollesis to the right, the weight of the body being shifted to the left. There was a partial ankylosis of the right knee joint with beginning atrophy of the muscles.

The skin was clear and covered with a normal growth of lange hair. The hair of the scalp was abundant coarse and dark brown and the cyclmous and cyclashes were normal. The palpebral fasures were equal and the pupils reacted promptly to light and accommodation. The ears, lips, mouth and tongue were normal. The deciduous teeth showed caries of the two upper middle incisors, as



Fig 2—L. Y (older brother)

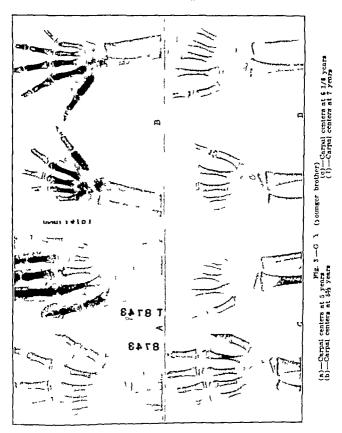
(a)—Carpal centers at 6% years

(b)—Carpal centers at 8 years

(c)—Carpal centers at 8% years

less than a year

well as of the right lower anterior molar. It may be added that subsequent examination of the teeth, when the boy was cleven years of age revealed earies of two of the four permanent first molars and of all the deciduous molars. The chest was symmetrical and the heart and lungs around. The abdomen revealed



nothing unusual. The genitals appeared to be underdeveloped but the testicles were fully descended. With the exception of the right lower extremity the limbs were normal. The nails of the fingurs and toes were dull in lustre but showed no fissures or furrows. The deep reflexes of the normal extremities were active. Mentally the boy appeared to be of average ability

During the course of observation, roentgenograms were taken of the various

bones and joints of the body. To our surprise, it was found that films showed only two centers of calcification of the carpal bones, despite the fact that the boy was over six years of age (Fig. 2A). This indicated a marked retardation in development of these centers, as, normally, at this age 6 to 7 centers should have been evident. All the metacarpal and phalangeal epiphyses were present. Roent genograms of the tarsal bones of both ankles revealed 6 and 7 centers, which corresponds to the norm for this age.

Case 2—(younger brother)—G Y In view of the retardation in development of the carpal centers of L it was thought advisable to take roentgenograms of the wrists of the younger brother, who at this time was 4 years and 4 months of age Films showed a similar retardation in the process of calcification in that only two centers and the beginning of a third, were to be seen in either wrist (Fig 3 A) According to the standards of Pryor, a boy of this age should have 4 or more carpal centers showing calcification. The metacarpal and phalangeal epiphyses were present. Roentgenograms of the tarsal bones showed normal calcification.

TABLE II

DATA IN REGARD TO DEVELOPMENT OF THE YOUNGER BROTHER (G)

FIGURE	DATE	AGE	WEIGHT	неіснт	COMPARISON WITH	1 .	BER OF CENTERS
FIGUL E	DATE	(YEARS)	(POUNDS)	(INCHES)	BALDWIN WOOD STANDARDS	GEORGE	PRYOR'S STANDARD (MALE)
3a 3b 3c 3d	11/23/27 4/ 9/28 1/13/29 11/25/29 10/12/31	5 5% 6% 7 9		 45¾ 49 49¼ 53½	per cent +28 +18 +14 +8	3 3 & 4 5 6*	$   \begin{array}{c cccccccccccccccccccccccccccccccccc$

<sup>\*</sup>Distal ulnae not vet evident.

Inquiry into the developmental history of George showed that he was born at full term, November, 1922 Delivery was normal and the presentation cephalic. The birth weight was 7 pounds, 4 ounces. The birth-cry was strong and there were no convulsions or cyanosis. He was breast fed until 13 months of age, no additional food being added to the diet. The infant was then given orange juice, cereals, cooked fruit, vegetables and meats, but never any cod liver oil. His appetite was always poor. The motor development of this child proceeded at a more rapid tempo than that of his older brother. He sat up alone at about 6 months, never crawled, and was able to walk with support at 10 months and with out support at about 15 months. He spoke single words at one year and phrases at about two years. The first tooth crupted at 10 months. In general, he showed a much more rapid rate of development than his brother, a fact of interest in view of subsequent development of the carpal centers. He always enjoyed good health, although subject to occasional colds. Tonsillectomy and adenoidectomy were performed at 4 years of age.

Physical examination showed a rather well developed youngster weighing 40½ pounds and 40 inches tall. The circumferences of his head, chest and abdomen were 19½, 20¾ and 22 inches, respectively. His color was good, the subcutaneous tissue firm and the muscles somewhat flabby. He was a mouth breather and the facial expression was dull. The posture was faulty, shoulders stooping, scapulae winged and the abdomen protuberant. The hips were rather wide and there was some degree of knock knee. The genitals were small and the penis retracted, but

both testicles were fully descended. There was a considerable amount of fat over the suprapuble region. The skin was soft smooth and had normal lanugo hair. The hands were small and the flugers thin and tapering. The nails were normal but of dull appearance. The entire picture suggested a Freehilch type. In fact, when the boy was about seven years of age he was observed elsewhere and considered a case of glandular desern in and was given glandular therapy, but with out apparent improvement in general physical state. At that time a basal metabolism test was made and was recorded as +9. He did poorly in school, his memory being poor he failed of promotion. Socially and at play he preferred to associate with much younger children.

The face was full and round. The hair of the scalp was dark brown and course, the cyclrows and evelaties were normal. The palphral fissures were equal and the pupils reacted normally to light and accommodation. Subsequent examination, at 0 years of age revealed a marked impairment of visual senity, the vision being 20/100 for both eyes. The care nose and threat were normal. There were 20 decidious teeth, showing poor cannel and wide spacing the occlusion was good. Although at 4 years of age caries had not developed examination at 7 years showed carious involvement of all deciduous molars. At 9 years the four permanent first molars were still sound. The neck was normal there was no adenopathy. The chest was som what flat anteroposteriorly. The heart lungs and abdomen were normal. The reflexes both superficial and deep were equal and active.

Summary -These histories may be summarized by the statement that the rate of development of the carpal centers of the older brother, L was not only remarkably slow but was striking in the manner in which the retardation was corrected. As late as 8 years of age but two centers had appeared at the wrist and no progress had been made in this respect for two years. Suddenly during the ninth year, from winter to autumn, a spurt in ossification came about. Films taken in November of this year revealed the presence of 5 centers in the left and 6 in the right wrist in addition to new centers at the distal ends of the ulnae, the appearance of which had been delayed by approxi mately two years. No adequate explanation can be suggested to explain this sudden increase in ossification. The boy's height had re mained the same, but his weight had increased 6 pounds and there was an undoubted improvement in his general condition. The vounger boy G was never so marked a case of carpal retardation having 3 carpal centers instead of 5 or 6 at five years of age. He caught up to the normal gradually, so that at seven years he approached closely to the standard except for a delay of the distal epiphyses of the ulnae Whereas L was somewhat below the average for height-weight age G was somewhat above, tending to be stout. His metabolic rate how ever, was slightly above rather than below the average. It may be added, that the development of the carpal centers of both parents appeared normal

#### DISCUSSION

It is true that variations may be noted in the development of carpal centers, a variability which is not great and, in our experience is nullified by the second or third year of life. Some years ago it was shown

by Hess and Weinstock' that even at the time of birth two centers occasionally may be noted. It is also true, as noted at our institution, that there is a similarity between brothers and sisters in regard to the rate and stage of carpal development The marked retardation observed in these brothers emphasizes the fact that congenital and constitutional factors play a rôle and must be considered in studies bearing on the physiology and pathology of calcification and ossification In the paper just referred to the rôle of constitution was further emphasized by the fact that the carpal centers of negro infants, at birth, were further developed than those of white infants A similar constitutional variation has also been brought out recently by one of us in connection with the susceptibility to rickets of puppies of different breeds2, one breed being more susceptible than another words, in experimental as well as in clinical rickets there may be a definite constitutional tendency to rickets, quite apart from diet, hy-This must be evident to all who have carefully giene, and growth studied rickets in the clinic The interesting observation of Stettner to the effect that the carpal centers of urban children ossify earlier than those of rural children, may, perhaps, be interpreted in this way \*

This clinical observation also emphasizes the fact that although ossification of the skeleton depends on systemic factors, it is also dependent on one or more local factors As stated, the calcium and inorganic phosphorus titer of the blood in these infants was normal, 103 Ca and 42 mg P in the one boy, and 100 and 40 mg in the other The Ca × P product was well within normal limits Nevertheless, ossification was delayed for years and, in the case of the one came about suddenly in the course of a few months without apparent change attribute this delay, as well as its sudden correction, to the absence and to the rapid development of a local factor, of what may be termed a mordant or "Kalkfaenger" Without taking cognizance of a local factor of this kind, no satisfactory explanation is possible of "high phosphorus rickets" in infants Occasionally, but by no means rarely, rickets develops in spite of approximately normal concentrations of calcium and inorganic phosphorus in the blood and a normal Ca × P We have observed numerous cases of this kind, especially among young infants The same may hold true for "rat rickets" In chickens it is very common to find calcium concentrations of over 10 mg, associated with phosphorus concentrations of 8 to 9 mg, in other words an exceedingly high Ca x P product, and nevertheless the noentgen rays as well as histologic examination show the typical lesions of rickets and the total ash is far below the normal level interesting phenomenon, unexplained, and of undoubted importance in the physiology of ossification as well as in the pathogenesis of disorders such as rickets, is further illustrated by the cases of carpal retardation which we have reported

#### CONCLUSIONS

An instance is reported of prolonged retardation in the development of the carpal centers in two brothers. A clinical observation of this kind is exceedingly rare and cains added interest due to the fact that it illustrates the rôle of congenital and constitutional factors in relation to essilication. As the concentration of calcium and in organic phosphorus of the blood was normal it would seem that a local calcifying factor a mordant or Kalkfaeuger was lacking In one of the cases the retardation was compensated suddenly during the ninth year within a period of a few months

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## ALIMENTARY TOXICOSIS

## Samuel Karelitz, M D New York, N Y

THE SUBJECT which I wish to discuss is one in which Czerny was a pioneer

Czerny¹ classified the nutritional disturbances of infancy on an etiologic basis under three headings ex alimentatione, ex infectione and e constitutione. The commonly accepted view of the etiology of alimentary toxicosis is that it is secondary to an infection, and so in Czerney's scheme it would be placed under the heading of ex infectione. This term signifies the following possibilities that bacteria decompose food, causing it to become injurious, that bacteria normally inhabiting the intestinal tract may, through putrefaction and fermentation of the intestinal contents, bring about the presence of toxic or irritating substance or may themselves become injurious, and that bacterial infection, regardless of the portal of entry or location, whether enteral or parenteral, may lead to a nutritional disorder. In brief, it includes the nutritional upsets which are the results of bacterial infection or the products of bacterial proliferation.

This view is probably a correct explanation for the majority of cases of toxicosis. Patients have been observed, however, whose histories indicated that other inciting factors were responsible for the disturbances which lead to toxicosis. With some exceptions, these cases etiologically would fall under Czerny's headings ex alimentatione and e constitutione. Thus, pure digestive disturbances such as those arising from overfeeding or from exceeding the tolerance for fat, abrupt weaning of an infant from its mother's milk, constitutional conditions such as inherent intolerence for carbohydrates and allergic idiosyncrasies to foods, summer heat, especially when associated with increased humidity, direct gastrointestinal irritation such as that induced by cathartics, all have been known to initiate the gastrointestinal disturbance which resulted in the development of toxicosis

Once the nutritional disturbance has been initiated, what brings about the toxicosis? The most convincing evidence points to the following explanations. The fluid (water plus minerals) loss, regardless of the manner in which it takes place, whether by diarrhea, vomiting insensible perspiration (ventilation through lungs and skin), or by these combined, leads to blood concentration, impaired circulation, diminished renal function, and acidosis, factors which are responsible for the intoxication. Most authors recognize the importance of these factors and some have attributed special significance to the acidosis and retention products due to the renal hypofunction.

Another explanation of the pathogenesis of toxicosis which has been championed extensively is based on its similarity to histamine shock. It has been suggested that the origin of these histamine like substances is the upper intestinal tract where coll bacilli have migrated from be low and caused partial splitting of proteins or by the disturbed intermediary metabolism, or from the injuried liver. It has also been suggested that the injury produced by these substances takes place because the liver has been damaged and is no longer able to perform its function of detoxification. The evidence for much of the above is still theoretical

To demonstrate our point of view on this subject the history abstracts of fifteen eases of toxicous presenting a variety of etiologic agents, and treated in the children's wards of Mt Sinai Hospital according to a plan previously described will be presented and briefly discussed

#### DISCUSSION OF CASE ABSTRACTS

Toxicosis ex Infections — Case 1 had a positive stool culture for the Flexner dysentery bacillus and thus represents an enteral infection Cases 2 to 5 were, respectively, due to mastoiditis, smallpox vaccination, pruria and pruria with recurrent upper respiratory infections. These illustrate toxicosis due to parenteral infection. It is noteworthy that in Case 5 patient was a breast fed infant. In the analysis of a group of 71 cases of toxicosis we found that infection was present in more than half. Undoubtedly some developed their infections after the diarrhea and vomiting had started. The Cases 1 to 5, however, illustrate a relatively common sequence, infection, gastro-intestinal disturbance toxicosis, and suggest a causal relationship between them

Toxicosis ex Alimentatione—Case 6 developed within three days after weaning from the breast to a simple formula of pasteurized milk, sugar, and water prepared under hygienic conditions. In Case 7 patient failed to thrive on cow's milk formulae and at eighteen days of age developed diarrhea which went on to toxicosis. In Case 8, patient was well except for slight constipation, until orange juice was started. She received an ounce of orange juice on the first day and promptly developed diarrhea. In absence of infection or other factors which may have initiated the diarrhea in these cases, we believe that they exemplify the development of nutritional disturbances exalimentation which progressed to toxicosis.

Toxicosis e Constitutione—Case 10 was a child with cyclic vomiting She vomited everything taken for a day, then developed diarrhea and rapidly went into toxicosis. In Case 11 patient while being treated for widespread eczema, lost twenty one ounces in two days and suddenly collapsed. He had vomited only a few times toxicosis super vened. These cases illustrate the constitutional predisposition which

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In the past few years the therapeutic procedure which we have employed? has had as its desideration the reestablishment of an adequate erculation and a rapid improvement of renal function. Coincident with this there occur detoxification correction of the acidosis, improvement of the tissue turgor, and a gradual disappearance of the gastro intestinal dysfunction.

It is worthy of note that as early as 1906 Geheimrat Czerny an nounced a classification of nutritional disorders on an etiologic basis that even today encompasses the preponderant number of instances of this illness.

CASE 1—II I #316095, Forth Rican male seven months of age Admitted July 31 1930 His birth and past listory were normal He was breest fed for two months then wenned on simple milk formula. He did well until three weeks before admis ion when he developed dilarrhen with fever of 1000 F On a ½ milk—½ barley water formula the diarrhen improved and the fever dropped. Two weeks later or five days before admis ion, the diarrhen recurred—14 to 10 stools daily With this the child was brought in collapsed, dehydrated and taxic. His temperature was 1000 F, he was drowsy his eyes were glassy his skin turgor poor his palse rapid and breathing slow and deep. The stools were bloody and on culture showed the Flexner type of dysentery bacillus. His blood CO content was 45 vol. per cent. He responded to treatment for toxicosis slowly. His progress was interrupted by an acute respiratory complication. He was discharged well in thirty days.

CARE 2-M M., #31,213, and 3184 3 was a nine month-old Irlsh female haby who weighed five pounds when born at term. She did fairly well on a simple milk formula and orange julce. At seven months of age Aug 7 1930, she was admitted to the hospital because of anorexia diarrhea and pyuria. She weighed 11 pounds. The diarrhea which did not respond to treatment with ordinary milk mixtures improved on protein milk. She was discharged as well after six weeks, with a formula of 20 ounces of milk 10 ounces of water, 114 tablespoons of cane sugar faring, orange julce and cod liver oil. A week later the child was readmitted because of acute rhinitis and severe diarrhea, vomiting temperature 103° F., and irritability She looked marantic and acutely ill. After a twelve-hour period of starvation and subcutaneous injections of saline solution she was started on a simple milk formula, and three days later it was changed to protein milk. She im proved Urine was normal. With onset of otitis media a week later the diarrhea recurred. The protein milk was reduced and the child was given two blood transfusions each of 110 cc. one week apart. The child continued to do poorly, the diarrhea continued the otitis media was worse, she lost a pound in twenty four hours. Mastoldectomy seemed indicated but was delayed because death seemed imminent On Oct. 20 she weighed 7 pounds, 2 ounces, temperature was 1050 F., color was ashen gray, pulse was very weak, skin turgor was extremely poor, she became dyapnele and she showed evidence of severe blood concentration and acidosis She was nine and one-half months old and weighed 7 pounds and 2 ounces. Treat ment for toxicosis was successful and no surgical intervention was needed for the otitic condition. At twelve months she weighed 12 pounds.

CARF 3.—O C., #3°0201 admitted Aug 18, 1931, was an eleven month-old Spanish female whose family history and past history were negative. She was normal at birth breast fed for three months and did well thereafter. She was never ill before. At ten months she received diphtheria toxin antitoxin and at

TABLE I LABORATORY DATA OF CASES REPORTED

	URINE	alb few WBC	neg	alb easts	Bou	alb pus		snd	W B C much pus	much pus much pus	alb W B C	neg
STIGAR	BLOOD					Serum	Fnosphorus 75	4 75				
JM	PROTEIN	%					<del>-</del> 4	58 51	7.0	63 76	4.7	58
SERUM	COOTENT	19 vol %	20	20	48	19.5	22	24 43	17	46 365	22	51
BL00D	URBA N			%		97 mg	18	2	58	93 33	75 36	18
PLASMA	NACL			% But 299	605	590	069	600 555	538	580 410	760	585
вгоор	R.B C			4560000	4880000	5500000			3650000		400000	4900000
Id	пав	66 08	66	70	76	8.2		7.0	70		102	95
	DATE	10/29/30	11/ 6/30	8/18/31 8/20/31	9/ 3/31	10/30/33	10/31/32	11/4/32 $11/15/32$	11/29/31	12/12/31 1/ 3/32	5/25/32 5/27/32 5/21/32	5/31/32
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ten and one half months she was vaccinated against smallpox. Nine days there after she began to have fever and simultaneously diarrhea

Her diet which consisted of whole milk (pasteurized), orange juice, vegetable and cereal, was reduced to barley and rice gruel

The temperature dropped in a few days, but the diarrhea continued, the stools were green and watery. Shortly thereafter the stools became very numerous, the fever recurred, and vomiting started

On admission to the hospital the child looked ashen gray and collapsed. Skin turgor was very poor, and she had marked hyperpnea and temperature of 105° F. Her eyes were sunken and her pulse was poor. The urine was scant, and contained albumin, a few granular casts and white blood cells. Blood chemistry revealed acidosis and hypoglycemia.

The vaccination was in scar stage and clean. No other evidence of infection was present. She recovered rapidly

Case 4—M K, #34420, admitted Oct 11, 1932, was an eight and one half month old female who was normal at birth and did well on artificial feeding until she was four months old when she developed a vaginal discharge. Gonococcal in fection was never demonstrated, nevertheless treatment was quite active with in ternal medication as well as local applications of antiseptic solutions. She developed pyuria with recurrent elevations of temperature. With her fever 100° to 102° F, she suffered anorexia and vomited frequently. Her weight remained stationary for two months. When she was eight months old, her stools became loose, her anorexia more marked and her general condition worse. She was admitted for study of the genitourinary tract. Intravenous urography revealed dilated ureters and calvees. The ps p test showed very poor excretion—15 per cent in three hours—but at a later time as much as 55 per cent in three hours. The blood chem istry was normal and the urine contained pus, but no casts or red blood cells. She vomited frequently, causing her weight to be stationary.

About five days after reflux urography was attempted, the child collapsed She became markedly hyperphete (70 respirations per minute), evanotic, her circulation was collapsed, skin turgor was poor, her dependent parts were mottled blue, and temperature mounted to 108 4° F She was unconscious, and had twitchings of the extremities, she was anuric, blood pressure was not elevated Blood showed evidence of severe acidosis, azotemia, and concentration.

Case 5—L B, #332765, a five month old Jewish female child was normal at birth and had thrived until five weeks before admission to the hospital, when she began to be irritable, restless and took the breast poorly. Stools became thinner and more frequent—5 to 6 daily—and she stopped gaining weight. About twenty four to forty eight hours before admission the stools became numerous, she refused to eat and became very ill. On admission she was drowsy, irritable, her cry was weak, her color gray, her eyes were sunken, her skin loose and pasty, of poor color, except over the lower extremities, hands and forearms, where the skin was edematous and pitted on pressure. She had deep hyperpnea and a poor pulse. The urine was scant and showed only few white blood cells. Blood showed evidence of marked acidosis, azotemia and some concentration. She improved under the treat ment for toxicosis. The pyuria persisted

On treatment as a case of toxicosis recovery was prompt. However, in forty eight hours she began to dribble purulent urine. Examination revealed a relaxed bladder and anal sphincter with some hypesthesia of the perineum. Rectal examination revealed a mass at the sacrum. Her knee jerks and abdominal reflexes were normal. The urinary tract was examined by various methods including in travenous pyelography and cystoscopy and revealed cystits. The mass felt by rectum grew and caused a defect in the sacrum, seen on roentgen ray examination.

The above episode recurred several times in the sub-equent ten months but was not accompanied by diarrhen. Comiting did occur once or twice a day. The same treatment was effective each time. Blood pressure was never elevated. Eye grounds were normal. Although she had the chronic pruria, no evidence of nephritis or renal insufficiency was demonstrable except for the oliguria during these recurrent episodes of toxicosis. She was found dead in hed without any apparent cause at affect months. Lostmortem examination revealed evaitits and a lipoma involving the sacrum and cauda coulan.

CASE C.—B. M. #339000 admitted May 2. 1932. A two-month-old Irish female child weighed "pounds S ounces at birth and 10 pounds 12 ounces four days prior to admission when she was weaned to a formula of 2½ ounces of milk 1½ ounces water and two teaspoons dextrimatione every three hours. The milk was grade A and boiled. She vomited the first feeding the formula was changed slightly but diarrhea started soon thereafter. The diarrhea was profuse a stool every fitten to thirty minutes, and continued so until the day before admission when the formula was changed again. However, the diarrhea continued and the child became drowsy. On admission she looked lethargle toxic gray. Respirations were deep and 54 per minute. Skin was motified and its turger very poor. The uring contained albumin, and the blood revealed concentration with acidosis and azotemia. On treatment for toxicosis she made a rapid and complete recovery.

CASE 7 —A S., #328913, was a male Italian twenty-six days old His birth weight was 7 pounds and he was a difficult feeding problem. On a formula of cow's milk, sugar and water he developed severe diarrhea at eighteen days and lost 2 pounds in the next week. On admission Aug 8 1931, he was ashen grav dehydrated thin marantic apathetic, and collapsed. His hands and feet were twitching A lumbar puncture revealed normal spinal fluid. He was treated with a saline solution clysus a blood transfusion and a small amount of formula of evaporated milk without success. His blood CO content was 12.5 vol. per cent, the NaCl was "02 mg per cent and the hemoglobin 92 per cent. Under the routine treatment for toxicosis he promptly improved excepting for the diarrhea which lasted seven days

CAME 8—B. G., #820472, admitted Aug 26 1931 A Porto Riean three months of age. She was breast fed for two months then weaned on a condened milk formula. She thrived but was constipated for which orange juice was recommended. A tablespoon of orange juice was given twice in one day The next day the child began to have diarrhea which had continued for the past two weeks increasing to 8 to 10 green watery stools daily She lost two pounds in that time and went progressively downhill.

On admission site was moderately ill, slightly lethargle, irritable Her eyes were lasterless. Her liver was 2.5 cm below the costal margin, and she had marked candiotabes She was treated by starvation and subcutaneous saline injection for about twenty four hours, during which time she became collapsed Replication became slow and deep, and the blood showed marked concentration and acidosis and evidence of rickets. Treatment for toxicosis was instituted, and after a stormy course for three days with almost constant convulsions, she improved and made a complete recovery During the convulsive state her Chrostek reaction was quite active and 10 c.c. of calcium gluconate given intravenously caused no improvement. A lumbar puncture revealed xanthochromic fluid

CARE 9—R. B, #335006 admitted Fob 6, 1932, was a Jewish female fifteen months old, who was normal at birth and did well except for two episodes of recurrent vomiting at three months and again at six months of age. Both were

stopped by enemata. She developed well, had been vaccinated and injected with diphtheria toxin antitoxin

Three days prior to admission she suddenly began vomiting everything, including water. The next day her temperature rose to 102° F, and diarrhea started. She had 5 or 6 loose stools in twenty four hours and then became quite drowsy. Tempera ture rose to 104° F, color became gray, eyes sunken, skin turgor poor, pulse very rapid and weak, and respirations quite slow and deep. A diagnosis of toxicosis was made, and she was promptly treated with success. Urine contained albumin, acctone and an occasional white blood cells. Blood revealed a lowered CO<sub>2</sub> content, diminished sodium chloride, and a somewhat elevated blood sugar.

Case 10—R J, #318774, admitted Sept 27, 1930. A Porto Rican eight month old male child admitted because of eczema which had appeared at three months of age when he was weaned, and covered his entire body. He had pertussis at six months of age. While in the hospital being treated with a tar ointment, he was fed a simple formula of pasteurized milk, cereal, and orange juice, a diet similar to that which he had had at home. His entire body was covered with this ointment for a few days. The eczema improved, but anorexia developed. Treatment for cerema was stopped. He vomited two or three times in the next four days and lost twenty one ounces. He was found in collapsed condition, skin turgor was poor, eyes were sunken, breathing rapid and labored, and pulse very poor. He was in a semistuperous state. Treatment for toxicosis was instituted with prompt improvement.

Case 11—M McK, #328830, admitted Aug 6, 1931. A two month old Irish female was normal at birth at term weighing 7 pounds 2 ounces. She was exclusively breast fed for three weeks and continued to thrive on a complimentary formula of 12 ounces of grade A milk, 8 ounces of water and 1 ounce of sugar Orange juice was started at one month. Eighteen hours before admission, during very hot humid weather, she began to have diarrhea. She had 12 loose, foul smelling stools in that period. Barley water was ordered in place of milk, but vomiting followed and the diarrhea continued. On admission she was collapsed and toxic, temperature was 102° F, skin was gray, mottled, and of poor turgor, eyes were sunken, and she was lethargic and markedly hyperpneic. There was no evidence of infection. Physical examination revealed no infection. The blood showed evidence of acidosis. The stool culture showed Bacillus proteus and Bacillus coli. She re sponded to the treatment for toxicosis.

Case 12—F P, #329631, an eleven month old Porto Rican female was admitted during the hot spell, on Aug 31, 1931—She was prematurely born and weighed 3 pounds 3 ounces—She was breast fed for three weeks, then fed an evaporated milk formula until six months of age, and since then 6 ounces of grade A milk and 2 ounces of water four or five times a day, cereal, occasionally orange juice but no cod liver oil—For the past two days for no apparent reason, the child began to have diarrhea—12 stools daily—and vomited a few times—In the past twelve hours she had become quite drowsy—On admission she was very ill, pale, eyes were sunken, skin turgor was poor, abdomen scaphoid, and breathing very slow and deep, pulse was very weak—There was no evidence of infection—Blood showed evidence of anemia, severe acidosis, azotemia, and blood concentration—The stool culture showed Bacillus coli—She did well on the treatment for toxicosis

Case 13—J C, #336294, admitted March 13, 1932, was normal at birth, weighing 10 pounds. He was breast fed for three and one half months and did well. Since then he thrived on a formula of milk and catmeal water. He had no orange juice or cod liver oil. Two weeks before admission he began his first illness with coughing. After the first week he improved, only to get worse again two days

later with heavy breathing paroxysmal cough and occasionally vomiting and tem perature of 100 F. Because of the productions of mucus with the cough caster oll was given and in the subsequent twenty four hours the child developed severe distribed. He was admitted the next day with temperature of 100 F., neutely ill. markedly dehydrated moderately toxic ever nunken, fontanelle depressed and the skin turger very poor. He was hyperpacie coughed and had duliness and rûles at the left base which proved to be due to pulmonary involvement, on reenigen ray examination. Blood showed evidence of pridosis and blood concentration and the urine contained allumin. He responded well to the treatment of textessis without a blood transfusion. The rise in temperature lasted only three days

Cast 14 - V M., #343 G., a five-month-old Irish female child was admitted on Sept 23 1932, because of diarrhen for one week. It had started after a dose of milk of magnesia given to her because the previous few stools were too firm. She was quite sick, apathetic and irritable. Her skin turger was poor the even sunken the fontanelle depressed and the pulse poor. Blood showed evidence of marked concentration, mild acide-is and arotemia and hypoglycemia. Her stool culture vielded Bacilius coli enterococcu. I rine showed some albumin and an excess of white blood cells. She was treated as a cas of toxicosis with prompt and progressive improvement

Casr 15-1 R., #34 381, admitted Nov 6, 1932 A five-and-one half month old Jowlsh female was admitted because of periodic abdominal cramplike prins, vom iting and bloody diarrhen for forty three hours. She was in poor condition but was operated upon for intus-usception which was found at the cecum and released Having been breast fed exclusively she was then fed small amounts of milk ob tained from her mother. Her condition was fair for a few days. She then developed upper abdominal distention vomited bile-stained material, and passed very little gas and no stool by rectum. The temperature fluctuated from 101 to 105. F. Blood culture was sterile. She became toxic eyes were sunken color gray, skin turgor poor, ery weak and pulse very poor. The epigastrium was distended. Blood showed evidence of concentration and axotemia, but no acidosis. She probably had intestinal and gastric atony. She was treated as a case of toxicosis except that her stomach was lavaged about eight or ten times in four days, with progressively diminished evidence of retention. She recovered promptly and completely under this treatment. Blood CO, content dropped from or to 38 vol. per cent after two days of treatment.

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1097 PARK AVENUE.

# MEASLES IN NEWBORN INFANTS (MATERNAL INFECTION)

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FOUR cases of measles in young infants who were infected by their mothers have been treated in the last two years at the Willard Parker Hospital. The ages of these infants at the time of onset of measles was fourteen, fourteen, and thirty days, and ten weeks, respectively. In two of the cases, therefore, the mother was incubating measles at the time of the birth of the child. Both of these children were born in institutions. In one case, the mother's flist day of fever was five days postpartum, and in the second three days postpartum. The offspring had fever on the ninth and tenth day, respectively, after the onset of the mother's illness. The following day, Koplik spots and other clinical signs of measles were noted in both infants. The day after, the rash appeared

The incubation period of measles is usually given as from eleven to fourteen days after exposure. This incubation period takes into consideration only the first appearance of clinical symptoms, such as cough, coryza or the first appearance of the rash. However, if the child is in an institution at the time of exposure, or soon thereafter, the temperature is taken regularly, and the first day of fever may be considered the day of onset. This temperature rise occurs about the ninth or tenth day after exposure and this may be called the true incubation time

In Cases 3 and 4 the mothers were exposed to measles postpartum In Case 3, the mother's exposure took place eleven days postpartum Twelve days later she had her first symptoms. Eleven days after, when mother and child were admitted to the hospital, the child already had fever and a few Koplik spots. In case four, the time of the mother's exposure was not known. Her first symptoms of measles were present three days before her admission to the hospital. Eleven days later the child developed fever. The next day Koplik spots were seen.

It seems, therefore, that the incubation period of the children whose mothers were incubating measles at the time of birth and those that were infected postpartum is about the same. The first day of fever was from nine to eleven days after exposure

The clinical course of the measles in these infants apparently differed in no way from that seen later in the first year. In case one, the child received convalescent serum on the seventh day after exposure. The course of the measles was mild. In this case it can haidly be considered

From the Willard Parker Hospital for Contagious Diseases. Dept. of Hospitals New York City

TABLE 1

CABE	BOEN		TRAT	TION OF	AT TIME OF	COLERE OF
NO.	BUES	MOTHER		CHILD	MEABLES	MEVERE
1	4/16	4/21	4/30	9 1)	14 D	Not very sick
2	2/29	3/3	3/13	10 D	14 D	Very siek
	]	-/ -	.,	1	j	Otitle, Pacumonia
3	3/8	3/281	4/ 71	10 D f	30 D	Quite sick
	(	( )		{	Ì	I neumonia
4	1/13	3/131	1/14	11 D f	10 W	Quito sick
	}	1		į	ļ	Otitis media
_	<b>.</b> .	1		(	į.	[i'ncumonia
5	1/2	12/26		)	]	Mother had full rash at
	}			}	;	birth Child isolated
	ł	!		}	1	Immediately No se
	}	]		)	1	rum given No
G				}	1	mensles
6	3/14	3/8	ĺ	ļ		Rash receding when
	1	}	}	1	{	child was horn Se-
	i					rum given when 1 day old No isola
	}	1	1	1	1	tion. No mensics
7	1/23	1/26	ł	ł	ł	First clinical sign of
•	1720	1/20	ļ	ŀ	ì	mensies 8 days post
	]	ļ	{	1	l	partum Serum gir
	ì	}	Ì	ì	l	en 8 days later No
	Í	{	(	(	{	measles
8	11/20/32	2/23	3/10	15 24 1	4 30	Whole blood given 9
	Į.		1	1		days after exposure
	J	)	}	į.	ì	Mild

D-Day

proof of the efficacy of convalescent scrum as the correct time for giving scrum is within five to six days after exposure. In the other three cases in which scrum was not given, the children were seriously ill All three had symptoms and signs of pulmonary involvement and two developed a purulent otitis media. The fever insted from ten to eighteen days after the onset. All of the children recovered

There were three additional cases, none of which developed measles that should be included in this series

Two cases (No 5 and 6) can be considered together. Both children were born while the mother had clinical signs of measles. In Case 5, the child was born when the mother's rash was at the maximum stage. The newborn showed no clinical evidence of measles. No convalescent serum was given, but the child was immediately isolated from the mother. The isolation was maintained until the child was ten days old. The child did not become infected. In Case 6 the child was born while the mother's rash was receding that is about two days after the maximum stage. This latter child also showed no clinical signs of measles at birth. The child was given convalescent serum soon after birth and was not isolated from the mother. This infant also remained free of measles.

In Case 7 the mother was incubating measles when the child was born. Her first day of fever was three days postpartum, but she had no

<sup>11-11</sup> eek

M-Month

clinical signs of measles until six days later, when for the first time her temperature was over  $38.5^{\circ}$  C ( $101^{\circ}$  F) The child was given 10 c c of measles convalescent serum when seventeen days old. This was eight days after the mother's first symptoms. Although the serum was given late, the child remained free of measles.

#### COMMENT

As has been shown by Herrman¹ and others, when a mother has had measles previous to pregnancy, her infant usually has an immunity for at least the first five months of life. This immunity is presumably transmitted through the placental circulation. It is often stated that if the mother has not had measles, the child has no such immunity. Since in most large communities the mother has had measles during childhood, measles in very young infants is infrequent. But this rule of immunity is not infallible, and there must be differences in individuals. I observed one infant three months of age, exposed to measles in the mother, who did not contract the disease. No convalescent serum was given. This child has been followed for seven years and up to the present time has not had measles.

A review of the literature of congenital measles, or the measles of early infancy is unnecessary. This has been adequately done by Reuss,2 Canelli,3 Mariani,4 Debie and Joannon6 and others These authors report cases in which the mother had measles a few days before expected delivery In most of the eases the child had clinical signs of measles at birth The measles was usually at the same stage as that of the mother In some cases, however, the measles would be at a later stage This suggests that the fetus is infected at the same time as the mother or is infected during her incubation period. This, however, was not our experience In the two cases in which the children were born while the mother's measles was still active, neither child showed any evidence of having been infected in utero. Immediately after birth, one was given convalescent serum and allowed to remain with its mother, while the other was given no serum but was isolated. They both remained free of infection Reuss2 cites a case of Koht in which a child had symptoms of measles five days postpurtum, which was eight days after the onset of the mother's infection. se reported by Laur the mother had symptoms the day after big. the child's first symptoms appeared when it was eight days old Reuss also cites a case of Moser, in which the child was born after the mother's rash had faded and the child had its first symptoms fourteen days postpartum. In the three cases reported in this paper, in which the mother was incubating measles at the time of birth, two were subsequently infected. In one, the first day of fever was nine days, and in the other, ten days after maternal exposure The giving of a large quantity of convalescent serum may have protected

the third patient. The east of Moser and those cases here reported were probably infected postpartium

If the mensles occurs before the cighth month of pregnancy the likeli hood of a miscarriage or premature birth is great. This usually occurs at the height of the cruption. In such cases the fetus has been found to have a rash at about the same stage as that of the mother. Gutwirth states that if the mother does not miscarry the offspring acquires a permanent immunity. Mariani cites several cases in which such off spring have been repeatedly exposed to measles and no infection has resulted. It would be interesting therefore to follow the cases here reported in which the infants were born while the mothers were still in the contradiction to this are the well-known cases in the Paroe Islands. During an epidemic of measles in these islands in 1846, a number of pregnant women were infected. The islands were practically free from measles until 1882, thirty six years later. At that time a number of the offspring of these pregnancies contracted measles.

The clinical course of measles in these voung children infected by their mothers is usually severe. Mortality statistics comparable to the cases here described are very meager. Figures given by Debre and loainons and Marianis show that the mortality is about 15 per cent. It seems logical, therefore, in order to modify its severity, that measles convalescent serum or adequate amounts of whole blood or serum from adults previously infected with measles should be given soon after exposure. It is known that in older children if immune serum is given within five or six days after exposure, the measles may be aborted or the resultant measles may be mild. Up to the present time except for the case (No. 6) here reported. I know of no newborn children infected by their mothers who have been given convalescent serum within five days after exposure. One cannot say with certainty therefore that this treatment will be efficient.

There is reason to believe that immune reactions in young infants are not the same as those occurring in older children. This is illustrated by diphtheria in young infants. It is usually serious and infants do not respond to treatment with autitoxin even when it is given early in the disease. Brindeau\* cites an epidemic of puerperal fever for which the diphtheria bacillus was responsible and states that nine infants were infected and all but one died notwithstanding antitoxin treatment. After this he injected each infant at birth with diphtheria antitoxin and the epidemic was arrested at once. Rabedeau Dumas Loiseau and Lacommo and others have attempted immunization of infants under four months of age with diphtheria toxoid and toxin antitoxin, but have been unsuccessful. The Schick test six months later was positive and the immunization had to be repeated in the second half of the first year.

The injection of toxoid into pregnant women did not influence the antitoxin content of the newborn Whether this analogy can be carried over to measles can only be decided with a wide experience

### SUMMARY

- 1 Four cases of measles in young children infected by their mothers are reported. In two of the cases the mother was incubating measles at the time of the birth of the child
- 2 In one other case, in which the mother was incubating measles at the time of birth, the child was evidently protected by convalescent sermm
- 3 Two children were born while the mother was in the eruptive stage Immediately after birth, one received convalescent serum and was allowed to remain with its mother, and the other received no serum, but was isolated Both remained free of measles
- 4 Congenital measles and measles in early infancy has been discussed
- 5 Since the course of the measles in young infants is usually severe the use of measles immune serum soon after exposure is indicated

Note -An additional case (No 8) was observed after this manuscript had been completed A child three months old was exposed to measles by the mother father had had measles, and the child was given 25 cc of his blood, nine days Fifteen days later the child showed symptoms of what proved to be modified measles

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## OBSERVATIONS ON THE NATURE AND TREATMENT OF DIARRHEA AND THE ASSOCIATED SYSTEMIC DISTURBANCES

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THE large amount of work which has been done during recent years on the subject of infantile diarrhea and its effects on the body has served to bring out essential facts which have formed the basis for prophylaxis and treatment. The numerous discussions as to whether infantile diarrhea is due primarily to abnormal chemical composition of the food, to nutritional disturbances to enteral infections or to parenteral infections have made it evident that there is no one cause of the condition, but that it may be due to any one or more of the factors mentioned, either alone or in combination with other fac tors. It has also become apparent that the severe toxic symptoms, the so-called "alimentary intoxication," are the secondary results of dis turbance in the chemical combirium of the body brought about as the result of loss of water, salts and organic material by way of the gas trointestinal tract, and that the development of the clinical picture of intoxication depends more upon the degree and severity of the diar rhea than upon the nature of the underlying cause. Any severe diar rhea, whether occurring as the result of enteral or parenteral infec tion, or other causes, may be associated with the development of the symptoms of 'intoxication The picture may of course, be compli cated by the direct effects of any infection which is present

The present day clinical picture of diarrhea and its complications differs materially from that of a decade or two ago. General improve ment in milk and water supplies and more adequate supervision of infants and the education of mothers have resulted in a greatly decreased incidence of the specific enteral infections (dysentery). A bet ter knowledge of the nutritional requirements of infants has resulted in generally better nutrition among infants, so that the effects of diarrhea are less serious. A better understanding of the nature of the condition and associated changes brought about in the body has resulted in a more intelligent application of specific therapeutic procedures designed to restore normal conditions in the body. Severe manifestations are more frequently checked in their incipiency.

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The purpose of the present paper is to summarize observations which we have made during the three-year period 1930-32 on all cases of diarrhea observed in the St Louis Children's Hospital with the idea of determining the essential etiologic factors involved, and to evaluate the results of therapeutic procedures adopted

During the three-year period 318 cases of diarrhea were observed, and of these 118 or 37 per cent fell in the classification of enteral infections or dysentery, using the term in its broadest sense to include not only in fection with the recognized strains of dysentery, but also closely related organisms of the dysentery-paratyphoid-colon group generally recognized as pathogenic As dysentery were included all cases in which specific pathogenic organisms were isolated, either from the stools during life or from the intestinal tract at autopsy, all cases in which specific agglutinins to the members of the dysentery-paratyphoid-colon group were demonstrated in the blood, and all cases in which there was clinical evidence of dysentery, such as blood or pus in the stools or a history of proved coincident familial infection though all doubtful cases were included in the dysentery group, the relative incidence of dysentery is seen to be low as compared with other types of diarrhea These figures differ materially from those of observers in other localities1, 2 3 during the same years observed the usual seasonal incidence, cases of this type beginning to be numerous in June and increasing in numbers to a peak in August and September, rapidly decreasing in numbers with the beginning of (See Chart 1) n mter

In the series of cases classified as dysentery, parenteral infections occurred during the course of the disease and complicated the picture in 66 per cent of the cases. The most frequent infections were bronchopneumonia, otitis media, mastoiditis and pyelitis. The mortality in the group with complicating secondary infections was 28 per cent, in those uncomplicated by such infections, 10 per cent. The occurrence of dysenteric infection seemed to bear but little relationship to the state of nutrition of the infants, dysentery was observed in well nourished as well as in poorly nourished infants. Very few of the dysentery patients had been under adequate medical supervision, or were from homes in which there was an intelligent appreciation of hygiene

The cases of nondvsenteric diarrhea were most frequently observed during the early fall months in the case of infants whose nutrition had suffered during the summer season and who, with the beginning of fall, contracted upper respiratory infections which served as the final precipitating factor. The seasonal incidence differed somewhat from that of the dysentery cases. Some increase occurred during the warmer seasons of the year, and the symptoms were somewhat more severe in excessively hot weather, presumably because of the influence of

heat in favoring further deliveration, but a fair number of cases oc curred even during the winter months when there were no cases of disentery (See Chart 1)

In the group of cases of simple diarrhea definitely recognizable parenteral infections in the rhimopharying, cars and mastoids were present in 83 per cent at the time of admission to the hospital. The incidence of such parenteral infections has however varied from year to year. During one fall and winter season previous to the present studies acute middle car or mastoid infections immediately preceded the development of diarrhea in 93 per cent of the cases. The incidence of parenteral infection was really somewhat greater than the figures given would indicate. Not infrequently in the case of infants admitted to the hospital in a state of severy dehydration, the presence of middle car infections was unsuspected because of lack of evidence of

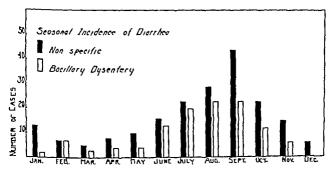


Chart 1 - Seasonal inclience of a respecific diarrhea and dysentery

inflammatory change in the tympanic membranes. With the restoration of the fluid balance and consequent improvement of the circulation, the tympanic membrane showed changes definitely indicative of infection, and this was confirmed by the obtaining of pus on paracentesis

Nondysenteric diarrhea was observed much more frequently in un dernourished infants, the course was more severe, the secondary toxic manifestations were more marked and the mortality was higher than in the case of well nourished infants. The most frequent feeding error preceding the development of diarrhea was quantitative or qualitative underfeeding which had led to impairment of the nutrition and apparently to lack of resistance to infection. The severe types of diarrhea were observed almost exclusively in artificially fed infants and in those who had received relatively dilute formulas of unacidified milk.

The mortality in the group of cases associated with parenteral in fections was 35 per cent, over three-fourths of the deaths (774 per

cent) being directly attributable to the complicating infections rather than to the effects of the diarrhea per se

There still remained a small group of cases (17 per cent) in which neither enteral nor parenteral infections could be demonstrated. The cases in this group were characterized by a short duration of the diarrhea (average four days) and a low mortality (5 per cent), as compared with an average duration of fifteen days and a mortality of 35 per cent in the group with parenteral infections

A study was made of the acidity and bacterial flora of the gastric contents in 200 of the cases of diarrhea of various types. In making

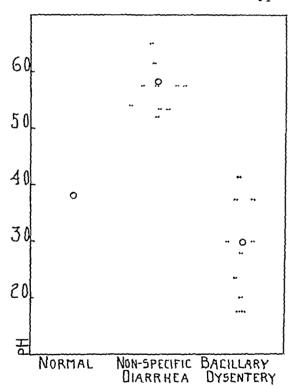


Chart 2—Hidiogen ion concentration of gastric contents Each dot represents one infant. Circle represents the average for age group

the observations, each infant was first given a test meal consisting of a 1-1 dilution of boiled whole cow's milk with water. Gastric contents were removed by catheter one and one half hours after the ingestion of the test meal. All samples containing mucus were discarded. Successive observations were made at the same time each day to note the effects of various feedings and other factors on the acidity and bacterial flora of the gastric contents.

The hydrogen ion concentiation of the gastiic contents was determined by the method previously described by Marriott and Davidson's

and bacterial cultures were made on each sample. The results were compared with those obtained from a group of normal infants under the same conditions. The  $P_{\rm H}$  of the matter contents of normal infants averaged 3.70 with extreme variations from 2.0 to 5.0. The results are expressed in graphic form in Chart 2. In the group of cases of non dysenteric diarrhea, there was a distinct lowering of acidity, the average  $P_{\rm H}$  being 5.65 and the extreme variation from 4.6 to 6.5. (See Chart 2.)

The acidity of the Lastric contents of the cases in the dysentery group differed markedly from that of the nonspecific type associated with parenteral infections. Regardless of the age of the patient and of the specific organisms, there was a distinctly greater acidity, the average P<sub>11</sub> of the gastric contents being J0 only one third of the



Chart 3 -The incid nee of IL coll in the gastric contents at varying hydrogen ion concentrations

cases having a P<sub>n</sub> above this average value (Chart 2) The acidity of the gastric contents of the infants in this group was not only much higher than that observed in the noninfectious group, but also distinctly higher than that observed in the normal group. In some in stances at the very beginning of the symptoms of dysentery there was some lowering of acidity, but after the first day or so the acidity al most invariably increased

The bacterial flora obtained on culture of the gastric contents of both normal infants and those suffering from diarrhea almost always included staphylococci and often streptococci and yeasts. In none of the normal infants were any strains of the colon group observed. In 45 per cent of the cases of nondysenteric diarrhea, the predominant flora of the gastric contents consisted of strains of B coli. In a number of cases of parenteral infection associated with vomiting, B coli

were cultured from the gastric contents before symptoms of diarrhea had developed, but in all such cases diarrhea occurred shortly afterward

A fairly close relationship was found to exist between the degree of acidity of the gastric contents and the presence of organisms of the colon group. This relationship is shown graphically in Chart 3. It will be observed that with decreased acidity there occurs an increased incidence of B. coli.

In marked contrast were the bacteriologic findings in the cases of dysentery. In these cases with the usual high gastric acidity, the stomach contents were entirely sterile in a few instances, and in the remainder the only flora present were those observed in the case of normal infants. There was a significant absence of members of the colon group during the active course of the disease. During the third week of the disease in protracted cases and where the picture was complicated by severe infections and malnutrition, a decrease in acidity of the stomach contents associated with the presence of B coli was occasionally observed. In these cases, nondysenteric diarrhea appeared to have been superimposed upon a dysentery

Our findings on the bacterial flora of the gastric contents are confirmatory of the observations of others, of and lend support to the hypothesis of enterogenous infection of the upper intestinal tract as a causative factor in the production of diarrhea The observations on the relationship of gastric acidity to the presence of flora of the colon group indicate the possible mechanism of such enterogenous infections, and at the same time point the way to possible means of preven tion and treatment of this type of diarrhea We consider it probable that infestation of the duodenal and jejunal contents with B coli and related organisms is of greater pathogenic significance than the presence of these organisms in the gastric contents. The presence of such organisms in the stomach, we take merely as evidence of more or less massive infection of the duodenal contents and recognize the fact that even in the presence of duodenal infection and in the absence of re gurgitation, the stomach may be free from the organisms When they are present in the stomach, however, it is most unlikely that they should be absent from the duodenum As will be shown subsequently, it is possible through the feeding of buffered acid solutions to bring and maintain the gastric acidity to almost any desired degree within normal limits, and that such a procedure results in general in a disappearance of B coli and everts a favorable effect on the course of diarrhea of the nondisenteric type

So far we have considered only certain conditions existing in the intestinal tract in the presence of diarrhea. The general effects of diarrhea upon the body are of as great or greater importance

The failure to absorb ingested food substances and water from the intestinal tract and to reabsorb gastrointestinal secretions may lead

to serious disturbances in the body, the degree of which in an untreated case, is more or less directly proportional to the severity of the diarrhea. Such changes include. (1) dehydration (2) electrolyte imbalance and (3) starvation each of which may lead to secondary trains of disturbances, the resultant of which may be rapidly fatal

Apparently under normal conditions the total daily amount of gas trointestinal juices secreted and absorbed exceeds two- or threefold the fluid intake. The immediate source of water for these secretions is, of course, the blood plasma. When such secretions fail to be returned to the circulating blood, because of loss through diarrhea the volume of the plasma tends to diminish (anhydreima). Passage into the circulating blood of the intercellular fluid of the body and to a certain extent also the intracellular fluid particularly of the muscles may prevent for a time such shrinkage of plasma volume but when these reservoirs become exhausted, dehydration of both the tissues and the blood plasma results.

In addition to loss of fluid by way of the intestinal tract further water loss occurs as the result of evaporation from the skin and lungs A diminished blood volume particularly when associated with in creased viscosity due to the relative increase in the plasma protein concentration and cell volume results in a greatly diminished volume flow of the blood which in turn interferes with the normal function of the circulation in carrying oxygen and food substances to the cells and removing carbon dioxide and other waste products. Secretion of urine in particular may almost completely cease under such circum stances, and result in retention of urea and other waste products in the blood. During such periods of severe dehydration however there seems to occur a relatively much smaller reduction in the amount of secretion of gastrointestinal juices, a fact in keeping with the tend ency for continued secretion of gastric juice in the experimental ani mal dying from gastric fistula, and of pancreatic juice in the animal succumbing to the effects of continued loss of pancreatic juice by fistula or intubation of the pancreatic duct

Although perhaps the normal mixture of gastrointestinal secretions may have an electrolyte composition similar to that of the normal body fluids the loss of large amounts of gastrointestinal secretions by fistula or diarrhea almost invariably leads to electrolyte imbalance in the body fluids. This disturbance is usually such as to produce acido sis. Factors contributing to the production of acidosis are. (1) a greater loss of fixed base than fixed acid. (2) the inability of the kidneys to excrete enough fixed acid bound to ammonia to maintain a normal bicarbonate concentration in the blood, and (3) the occasional production of organic acids such as lactic acid and the ketone acids due to circulatory failure or to starvation. It should be remembered in this connection, that analysis of a blood sample at a time when

severe dehy dration exists sometimes fails to reveal loss of individual ions, i.e., there may be considerable chloride and fixed base lost from the body, and yet their concentrations in the plasma may be above normal. This is simply due to the fact that water has been lost from the plasma to an even greater degree. Recovery from such changes demands the proper administration, not only of water, but of chloride and base. When bicarbonate lowering is extreme (to  $\frac{1}{4}$  or less of the normal concentration) the acidosis is frequently uncompensated, and the  $P_H$  of the blood may drop to 7 or less. Such severe acidosis tends promptly to be fatal and demands very vigorous treatment. Detailed studies of the chemical composition of the blood of patients observed and treated in this clinic have been published previously  $^9$ 

In addition to the loss of water and electrolyte substances, there occurs a more or less rapid consumption of the body stores of carbohydrate, fat and protein, leading to emaciation, as well as to dehydra-Depletion of carbohydrate stores sometimes contributes to the development of acidosis in making ketosis possible Ketosis, however, is not an important consideration in the acidosis of acute diarrhea. except when the diarrhea is due to acute bacillary dysentery consumption of body protein, however, may frequently lead to serious secondary disturbances, particularly when the plasma proteins become depleted Such depletion, often masked during the period of dehydration, becomes manifest after restoration of body fluids, and contributes frequently to generalized edema, which quite aptly has been termed "nutritional edema" During the development of such edema, despite the fact that the kidneys may be essentially normal, there may occur marked oliguria, sufficient to impair seriously normal renal activity Such renal activity may in turn result in continued electrolyte imbal ance and interfere with recovery from acidosis or alkalosis

Effective treatment of the more severe cases of diarrhea must in clude prompt restoration of normal blood chemical composition and normal conditions in the gastrointestinal tract. Measures particularly directed toward one end frequently have a good effect on the other, and the two objectives cannot be sharply separated one from the other

In practice, we have found the following method of treatment to be the most effective (1) total restriction of food, (2) the administration of an isotonic solution of sodium r-lactate, sufficient to relieve promptly the acidosis and to relieve at least partially the dehydration 10 In the presence of severe acidosis, the usual dose of sodium lactate is 10 cc of a molar solution\* per kilogram of body weight,

Such molar solution may be obtained already prepared in 40 cc ampules (Eli Lilly and Company Indianapolis)

<sup>\*</sup>Molar sodium lactate may be prepared by neutralizing 100 c.c. of U S P lactic acid with concentrated sodium hydroxide, using phenol red as an indicator. The solution is made up to about \$00 c.c. with distilled water and heated to the boiling point for from thirty to forty-five minutes meanwhile adding small amounts of alkali as needed to neutralize the lactic acid formed through hydration of the anhydride. The solution is then made up to 1000 c.c. It may be sterilized in an autoclave and preserved in stoppered flacks or in scaled ampules.

diluted by the addition of 5 volumes of sterile distilled water. A part of this (one third to one-half) is injected intravenously, to restore as quickly as possible diminished blood volume, while the remainder is administered subcutaneously or intraperitonically, (3) administration of physiological buffer salts solution parenterally, (4) the adminis tration of dextrose solution to furnish fuel, to relieve ketosis and to help in re-establishing the glycogen reserves of the body solution in isotonic strength (6 per cent) may be given as such sub cutaneously or mixed with equal parts of physiologic buffer salts solu The dextrose may also to advantage be given by continuous slow intravenous injection For this purpose a 10 per cent solution, either alone or mixed with an equal volume of physiologic buffer salts solution, is used. The rate of injection of the 10 per cent solution of dextrose should not exceed 3 e c per kilogram of body weight per More rapid injection may result in glycosuria, edema, embar rassment of the circulation and at times to a general reaction with temperature elevation and chills (5) The administration of citrated whole blood This procedure should not be resorted to until after the fluid balance has been well restored, masmuch as transfusions given in the presence of marked blood concentration may result in a still fur ther merease in plasma protein content and an intensification of the phenomena of anhydremia

After the fluid content of the blood has been restored, blood trans fusion tends to reestablish the plasma protein level in the recipient when this is low as the result of poor nutrition or has been in part destroyed during the existence of anhydremia and is in consequence low when the blood volume has again been reestablished through the administration of fluid. Transfusion therefore tends to prevent the development of secondary nutritional edema. The administration of blood may furnish some bacterial antibodies, particularly to B. coli Transfusion of whole blood also furnishes red blood cells, which are capable of functioning normally, and in this way tends to prevent the development of anemia after dehydration has been overcome.

The above measures designed particularly to restore normal blood and body fluid volume and chemical composition, can usually be carried out satisfactorily within the first twelve hours. Should severe diarrhea continue, the parenteral administration of physiologic buffer salts solution may have to be repeated two or three times daily, or given continuously by the slow intravenous drip method.

During the period of food restriction, which should last for twelve to forty eight hours or more, depending upon whether or not diarrhea

The physiological buffer saits solution (Hartmann's solution) has been described classwhere. It is essentially a mixture of Ringer's solution and sodium inetate and is designed to supply potassium content and magnesium in addition to solium ions and chloride and enough potential blearbonate to prevent the recurrence of acidosis, should diarrhee continue. This solution is obtainable in ampule form. (Ell Lilly and Company Indianapolis.)

tends to continue despite food restriction, it seems of value to offer small amounts of acidified and buffered water, which tends to keep the stomach and upper intestines sufficiently acid to prevent the growth of intestinal organisms This buffered water is composed of lactic acid in 100 millimolai strength and sodium lactate in 50 millimolar strength. It is sometimes advantageous to sweeten this mixture with saccharine

After the preliminary starvation period, the most efficacious method of resuming feedings is to offer small amounts of Dryco (half-skimmed dried milk) or dried protein milk, diluted 1 to 10 with the above mentioned buffered mixture Very gradually, after the condition of the patient improves and the diarrhea becomes less, the amount of food may be increased We have found it satisfactory, first to concentrate somewhat the dried or protein milk dilution (making it 1 to 8) and then to add gradually the carbohydrate to the formula in the form of Kaio syrup (dextrin and maltose) When roughly 6 per cent carbohydrate has been added to such a formula and the patient is taking amounts of such a formula normal for his age, evaporated milk diluted with an equal volume of buffered solution or 1 per cent lactic acid, and with the addition of 5 to 7 per cent of carbohydrate may be substituted for the protein milk mixture and in this way adequate calories may easily be given

In general, the same measures found efficacious for the relief of dehydration and restoration of the normal chemical composition of the body fluids in the nondysenteric form of diarrhea were also found highly satisfactory in the more severe forms of acute bacillary dysen-Because of the much greater frequency of severe ketosis in dysentery, dextrose seems more specifically indicated, and should be supplied in addition to physiologic buffer salts solution, at least as long as ketosis is present. The preliminary restriction of food has also been The feeding of buffered water, however, seems found efficacious rarely necessary, because of the more normal secretion of gastric juice In regard to dietary measures, the most important point would seem to be the restriction of fat during the period of toxemia. It is our impression that feeding of milk formulas containing 3 per cent fat or more tends to increase vomiting and to make the stools larger and more waterv After vomiting has ceased and the temperature has become normal or almost normal, it has been our plan to increase the food rapidly, so that an adequate amount of calories may be given order not to interfere with the healing of the ulcers in the intestinal mucous membrane, the food should contain little or no roughage addition to an adequate amount of milk with or without added carbo-

<sup>\*</sup>This solution is prepared as follows 

hydrate, such food substances as Jello fruit junces strained cereal arrowroot crackers with butter and jelly have been found useful

In any case in which parenteral infection is present whether as the primary cause of the diarrhea or as a secondary complication, such meetion should receive appropriate treatment. The treatment of par enteral infections may include local treatment of the nose and throat, paracentesis of the ear drum or in those cases in which there is defi nite evidence of mastoid involvement, postauricular dramage or mas The latter procedure is rarely necessary except in toid antrotomy the case of epidemic streptococcus infections. When such infections are present, and are the primary cause of the diarrhea, excellent re sults are obtained following antrotomy. When infections of the mas toid or of the nasal accessors sinuses are secondars manifestations, operative treatment may also be indicated but this is not followed by the same striking results as in the case of primary parenteral infec After operation, the wounds heal slowly and the mortality is The diarrhea, not being dependent entirely upon the infection lugh may be but little influenced The purpose of treating the infections is to remove one of the complicating factors prejudicing recovery

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# A NOTE ON THE PATHOGENESIS OF RENAL RICKETS

DERANGEMENTS OF CALCIUM AND PHOSPHORUS METABOLISM IN NEPHRITIS

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RENAL dwarfism and renal rickets are terms which have come to be commonly employed to designate the retarded growth, skeletal deformities and osteoporotic changes observed in children suffering from marked renal insufficiency The association of late lickets with disease of the kidneys apparently was first noted by Lucas in 1883, and Fletcher in 1911 wrote the first clear description of a case of infantilism associated with chronic renal disease That the condition is being increasingly recognized in recent years is attested by the many case reports and papers which have appeared, treating renal rickets as a disease entity, reviews of this extensive literature may be found in the papers of Barber (1921), Hunt (1927), Parsons (1927), Apert (1928), Mitchell (1930), Swart (1930), and Maddox (1932) While the symptomatology and pathology of the condition have been thoroughly described many times, the fundamental mechanism responsible for the bone changes remains obscure The purpose of this paper is to present arguments in favor of an hypothesis which attempts to explain something of the derangement of mineral metabolism in chronic nephritis and to account for the faulty skeletal development Part of the material presented herein was incorporated in an earlier review [Mitchell (1930)] of Nephrosclerosis in Childhood mental studies along the lines indicated in this discussion are in progress and will be reported elsewhere in a later communication

In renal rickets the general symptoms are those of chronic nephrosclerosis, namely, polydipsia, polyuria, retarded development, wasting, pallor and secondary anemia. Acute symptoms of uremia of varying degree occur and recur from time to time, especially coincidentally with various intercurrent infections. The renal insufficiency in these cases is usually a consequence of chronic sclerotic nephritis, of cystic disease of the kidneys, or of obstructive congenital anomalies of the urinary tract. In most instances in which renal efficiency was tested the function was found to be markedly reduced, often as low as 1 per cent of normal (dve excretion) and with inability to concentrate the urine. Skeletal changes varying in degree develop as a rule about the age of puberty. The age of onset of marked symptoms in most

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cases is from ten to fourteen years, but cases in younger children are seen not infrequently. The bones of these children display a picture of poor calcification and osteoporosis of varying severity. On the basis of the roentgenologic picture Parsons (1927) divided his cases into groups designated the "atrophic" type, the "florid" type and the "woolly, or stippled" type respectively, but these types appear to represent varying degrees of osteoporosis rather than real qualitative differences in their pathologic changes. The chemical changes in the blood are those ordinarily associated with severe chronic nephritis that is, elevated nonprotein introgen, elevated morganic phosphorus, lowered serum calcium lowered bicarbonate and a tendency to acide in Explanation of the poor calcification of the bones in renal rickets

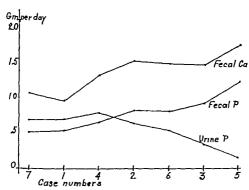


Fig. 1—Graphic representation of data taken from the studies of seven nephritic children reported by Bord Courtney and MacLachian (1926)

has been sought most often in the chemical changes of the blood, especially in the abnormal concentrations of calcium and phosphorus which are found in the blood serum

Increased morganic phosphorus in the blood in nephritis is generally stated to be due to inability of the kidneys to excrete the waste endogenous phosphates of the body but it must be recognized that the blood phosphorus level is not an index of the amount of phosphorus excretion or the lack of it and that an elevated blood phosphorus level is not a true measure of phosphorus retention. The real inability of diseased kidneys to excrete phosphorus can be more accurately evaluated if the efficiency of renal excretion of phosphorus is tested directly. Two studies may be cited in which such quantitative measurements have been made. Bolliger (1929) induced a form of slowly progressive sclerotic nephritis in dogs by exposing their kidneys to

high doses of roentgen rays. To test the renal efficiency for phosphorus excretion in these nephritic animals, he injected measured amounts of a buffered solution of sodium phosphate intravenously and determined the amount of phosphorus excreted in the urine during the succeeding two hours During the slow evolution (thirty to minety days) of renal sclerosis and loss of functioning kidney tissue which followed the irradiation of the kidneys, repeated tests showed a progressive decrease in the excietion of phosphates from around 80 per cent of the amount injected to a 'trace' Tests with phenolsulphone phthalem in the same animals showed a parallel decrease in the excretion of the dve Biam and Kav (1929) also devised a quantitative test of renal excretion of phosphates which they believed gave an index of renal function more significant than the usual dye excretion tests. In a series of normal persons and nephritic patients they de termined the hourly rate of urmary phosphorus excretion immediately before and immediately after the injection of a measured amount of sodium gly cerophosphate. In a group of patients with the diagnosis "chronic nephritis terminal stage" the urinary excretion of the in jected phosphate was markedly reduced to between nothing and 30 per cent of that amount excreted by the normal control group

In severe nephritis low serum calcium values have been found by Halverson Mohler and Bergeim (1917), Denis and Hobson (1923), de Wesselow (1923), Fetter (1923), Rabinowitch (1925), Schmitz, Rohdenburg and Myers (1926), Boyd, Courtney and MacLachlan (1926) and many others. Among these investigators there is general agreement that in nephritis the serum calcium exhibits roughly an inverse relationship to the inorganic phosphorus, that is, the serum calcium is usually low when the phosphorus is elevated Experimental evidence that inorganic phosphorus has a strong influence upon the level at which calcium is carried in the blood is furnished by experiments such as those of Binger (1917) and of Tisdall (1922) wherein it was demonstrated that in dogs the intravenous injection of phosphoric acid and its sodium salts caused a marked depression of the serum calcium Other factors, of course, play important rôles in governing the concentration of serum calcium, for example, a three-fold relationship of morganic phosphorus, calcium and total protein of the blood serum has been defined by the studies of Peters and Eiserson (1929)

Laying stress upon the observations of low serum calcium values in renal rickets several investigators have attempted to explain the faulty bone calcification in this condition by citing the hypothesis of Howland and Kramer (1921) that undersaturation of the blood serum with calcium phosphate might account for the bone changes of infantile rickets. According to the supporters of this hypothesis, the depression of serum calcium by the elevated morganic phosphorus found

in the blood in renal rickets may account for the failure of calcium to be deposited in the bones. The empiric (a x P product as used by Howland and Kramer to indicate the total concentration of calcium phosphate in the plasma has been used by different writers both to support and to discount that contention Parsons (1927) extended this argument by calculating (a x P ion products for some of his own cases and others collected from the literature and attempted to show that the values for such ion products would be found to be in the range observed in infantile rickets if the dissociation constants reported by Holt LaMer and Chown (192a) were used taking into ac count the lowered serum Pa values observed in most of these cases As an illustration of this he took data from a case in which Lathrop (1926) argued that the deformities were not true rickets because the Cax P product was above the raclatic level. Lathrop's data recalen lated with corrections for the very low scrum Pu value recorded in the published article gave an ion product compatible with true rick ets. Parsons however, took the single Pu determination (Pu 698) as characteristic of the reaction of this patient's blood while Lathrop's record indicates that this value was obtained at a time when this patient was in a state of acute acidosis verging on uremia certainly such a reaction could not have been characteristic of the blood of this patient in more normal periods

The studies of Hustings Murray and Schdroy (1927) and others indicate that the theory of supersaturation of the blood plasma with calcium phosphate is inadequate to explain the processes of normal bone calcification I ven granting however the possible significance of serum Ca v P products in infantile rickets, it is probable that in renal rickets the Ca x P ion products will always except perhaps in the presence of severe acidosis be above what may be believed to indicate a significant reduction in the degree of saturation of the plasma with calcium phosphate Since it seems unlikely that the actual concen tration of either calcium or phosphorus in the circulating blood of patients with renal rickets is ever too low to permit calcium deposi tion in the tissues, it would appear that the defective bone develop ment in this condition must be due to other underlying faults in infantile rickets the blood chemical changes may be interpreted only as secondary manifestations of the disorder similar to the grossly vis ible bone changes, the more fundamental fault is a failure of absorp tion of calcium and phosphorus from the food in the intestine this in mind it seems worth while to consider here a few factors which are known to affect the total calcium and phosphorus metabo ham of the body and especially the manner in which the absorption of calcium may be affected by certain conditions which develop in severe nephritis

Phosphorus is one of the most important of those waste products which are, in health, ordinarily excreted by the kidneys. Normally in children the urinary phosphates represent about 50 per cent of the phosphorus intake, and, of the total output, about two-thirds leaves the body in the urine and about one-third in the feces. Many factors and events concomitant with nephritis, such as intercurrent infections, acidosis, etc., are known to increase cell catabolism and the liberation of phosphorus from the body in amounts more than normally excreted. What, then, must be the conditions in severe nephritis with poor renal function when those waste endogenous phosphates cannot leave the body by the usual route of the kidney? Even in the most marked states of nephritic acidosis the increased amount of phosphorus in the blood is too small to indicate an accumulation of the large amounts of phosphates which are ordinarily excreted in the urine

Experimental studies of calcium and phosphorus metabolism furnish evidence that the intestine has the ability to secrete both calcium and phosphorus in considerable amounts [Beigeim (1926)] few published studies of calcium and phosphorus metabolism in nephritic children that are available, evidence also may be found that in nephritis with impaired renal function the intestinal secretion of phosphorus may be increased by the waste endogenous phosphates escapmg from the body through this route. That the increase of intestinal phosphates by such a change in the route of phosphorus excretion may indirectly have a deleterious effect can be surmised from the fact that these waste phosphates are in forms well suited for precipitating calcium in the intestinal tract. As will be noted in the succeeding paragraphs, even under normal conditions if the concentiation of phosphates in the intestine is greatly increased by a high phosphorus intake in the diet the absorption of calcium is interfered with, presumably by the formation of insoluble calcium phosphates intestinal contents have added to them those waste endogenous phosphates which ordinarily leave the body in the urine, a similar effect of diminished calcium absorption may well be expected excreted intestinal phosphates be in sufficient amount to interfere considerably with calcium absorption, it should also be expected that continued calcium deprivation will result in general systemic manifestations of a lack of calcium in the body. The argument that a disturbance of calcium metabolism of such a nature can occur and can account for the poor skeletal development seen in renal rickets is supported by various observations cited in the following paragraphs

Experimentally, rickets is easily produced in rats (in the absence of ultraviolet light or vitamin D) by diets which have either a high calcium and low phosphorus content or a low calcium and high phosphorus content. A high calcium, low phosphorus diet induces rickets in rats which is characterized by chemical changes in the blood similar to those found in human infantile rickets, namely, normal serum

calcium and low inorganic phosphorus. On the other hand, a low calcium, high phosphorus diet induces rickets characterized by low serum calcium and high inorganic phosphorus. Food metabolism studies done on such experimental animals make it apparent that a relative excess of either calcium or phosphorus in the diet will interfere with the absorption of the other from the intestine, by the formation of insoluble calcium phosphates which, unabsorbed, leave the body in the feces. It may be noted here that Shipley, Park, McCollium and Simmonds, in 1922, in a paper entitled '1s There More Than One Kind of Rickets?' discussed these two types of experimental rickets in relation to certain forms of rickets observed elimically and described a case of renal rickets in which they thought the changes resembled those of the low calcium 'type of rickets which they had induced in rats by the low calcium diet

In agreement with such observations in experimental animals there have been reported a few studies in normal human infants which indicate that here too an excessive intake of either calcium or phos phorus may interfere with the absorption of the other element from the intestine Of such studies, those of Orr Holt Wilkins and Boone (1934) are probably the clearest. They observed two infants during three metabolism periods of four days each with intervals of rest be tween, giving in the successive periods a normal diet a high calcium diet and a high phosphorus diet. With the high calcium diet more calcium was retained the scrum calcium rose where it had been low and more calcium was excreted in the urine phosphorus retention was diminished considerable amounts of phosphorus were diverted from the urine to the stools and the serum phosphorus was lowered With the high phosphorus diet there was no increase in the phosphorus retention and in one case the phosphorus retention diminished calcium retention was markedly decreased with a great increase in the fecal calcium and decrease of the urmary calcium. In one case there was a definite fall in the serum calcium

The studies of Boyd, Courtney and MacLachlan (1926) of calcium and phosphorus metabolism in nephritis furnish data which indicate that there was a changed route of phosphorus excretion in a group of nephritic children who seemingly had comparatively mild renal in pairment. In their group of fifteen children with nephritis of various types, the first seven cases were described as having no edema and having a tendency to elevation of the phosphorus and depression of the calcium in the blood serum, changes comparable to those found in patients with renal rickets. The data from these seven cases are presented graphically in Fig. 1 arranged in the order of increasing daily fecal phosphorus exerction and of decreasing urinary phosphorus exerction. Arranged thus without regard to other factors, it may be seen that there was roughly a reciprocal relationship between the amounts of phosphorus exercted in the urine and in the feces, and

that as the phosphorus excietion was greater in the feces the increasing amounts of calcium lost in the feces were about proportional to the increasing fecal phosphorus

In a study of calcium and phosphorus metabolism in a group of eleven nephritic children Ford (1931) found a similar deviation in the excretion of phosphorus from the unine to the feces, with losses of calcium in the feces closely parallel to the fecal excretion of phos phorus For comparison, Ford collected from several sources in the literature the data on calcium and phosphorus metabolism studies of twenty-two normal children In this group the fecal phosphorus amounted to 303 per cent of the intake and 392 per cent of the total output, the fecal calcium excretion was 647 per cent of the intake cr 91 per cent of the total output In Ford's group of eleven nephritic children (various diagnoses, and of varying severity of the nephritis) the fecal phosphorus was 542 per cent of the intake or 623 per cent of the total output, while the fecal calcium excretion was 78 per cent of the intake or 974 per cent of the total output "Thus, an increase, relative and absolute, is found in both the calcium and phosphorus contents of the feces, of which the increase in phosphorus is relatively the greater "

Data from mineral balance studies of three nephritic children, which were made available through the kindness of Dr L Schoenthal in a personal communication, also give evidence of an increased excretion of phosphorus in the feces. These figures were published in the review of nephrosclerosis previously cited [Mitchell (1930)]. During the period of study, in Schoenthal's patients the fecal phosphorus represented respectively 50 per cent, 65 per cent and 75 per cent of the total phosphorus output. In two of the children there was a negative phosphorus balance, with the fecal phosphorus amounting respectively to 90 6 per cent, and 112 9 per cent of the phosphorus intake. The child in whom the fecal phosphorus was actually in excess of the phosphorus intake during the period of study, was suffering from renal rickets, the case reported by Schoenthal and Burpee (1930).

As previously stated, many circumstances commonly arising in nephritis tend to increase cell catabolism and to liberate phosphorus from the body in amounts greater than normally excreted, and with poor renal function, all such factors make it more difficult for the nephritic child to maintain normal calcium and phosphorus metabolism. The intoxications of bacterial infections increase cell catabolism, and the nephritic is frequently thrown into mild or severe acidosis by various intercurrent infections which would be of slight significance to the person with normal kidneys. In subjects with normal renal function, states of acidosis induced in many ways are attended with marked phosphaturial carbon dioxide acidosis induced by rebreathing and the lactic acid acidosis of muscular exercise

[Havard and Reay (1926)], needosis induced by the injection of am monum chloride or other acid substances [Haldane, Hill and Luck (1923) and Morris (1930)] ketosis induced by a high fat low earbo hydrate diet [Nelson (1929)] diabetic acidosis [von Noorden (1907)] Haldane Wigglesworth and Woodrow (1924) and Kay (1924) showed that in ammonium chloride acidosis the labile organic acid soluble phosphorus-the so called ester phosphorus fraction-in the blood cells was markedly reduced and presumably was the source of a considerable part of the increased phosphate lost in the urinc mechanism by which the phosphates are released from the body in response to acidosis is not clear but it is significant that certain of the labile organic phosphorus compounds in the cells of the body tend to split readily to yield morganic phosphorus when the reaction of their surrounding fluids is changed even slightly toward increased acidity [Martland (1925)] In some studies of the behavior of phosphorus during glycolysis in blood taken from nephritic patients in severe states of acidosis, hydrolysis of the organic acid soluble phosphorus of the blood cells with liberation of morganic phosphorus has been observed to occur much more rapidly than in normal blood [Guest (1932) ] In the nephritic patient with marked renal insufficiency each of these various circumstances which results in increased liberation of phosphorus from the body may impose a further handicap upon the absorption of calcium if the extra phosphates are exercted into the bowel Parsons (1927) and others point out that in states of aci dosis there is also an increased mobilization of calcium stored in the Repeated transitory disturbances such as these can easily account for the picture of flux between healing and relapse ' which Shipley, Park McCollum and Simmonds (1922) described as charac teristic of the bone changes in renal rickets

Examples may be cited of substances other than phosphorus which interfere with absorption of calcium from the intestine, with consequent deleterious effects of calcium deprivation. It has been shown that high fat intake or poor utilization of fats and fatty acids results in the formation of insoluble calcium soaps in the intestine and in creased output of calcium in the feces [Lindberg (1917)]. Givens (1917) Sawyer Baumann and Stevens (1918). Holt Courtney and Fales (1920) and Telfer (1926). Such losses of calcium can account for the low calcium type of rickets and osteoporotic changes commonly observed in celiac disease as well as in other forms of chronic steator rhea. Parsons (1927) has described the gross similarities in the bone changes of renal rickets and celiac rickets.

#### SUMMARY

In types of nephritis characterized by relative mability of the kid news to excrete phosphates there exists a considerable amount of evidence that the waste endogenous phosphates of the body which are ordinarily found in the urine may be excieted through the bowel, and that the phosphates thereby increased in the intestinal contents can interfere with the absorption of calcium by the formation of insoluble calcium phosphates which, unabsorbed, leave the body in the feces It is suggested that long-continued partial starvation of calcium resulting from this metabolic fault is principally responsible for the condition known as renal rickets, that is, the low calcium type of rickets seen accompanying marked renal insufficiency in growing children

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## THE ALLIGLD CORRLLATION BETWEEN THE RATE OF GROWTH OF THE SUCKLING AND THE COMPOSITION OF THE MILK OF THE SPECIFS

### GROVER F POWERS, MD NEW HAVEN CONNECTICUT

DURING the last quarter of the Nineteenth (entury Professor Bunge<sup>2</sup> of Basel and his pupils Proscher<sup>2</sup> and Abderhalden (a.c., the came greatly interested in a relationship between the composition of milk, the composition of the body of the suckling and its rate of growth Attention was also called to the observation that as the suckling grows the composition of its tissues changes and that a corresponding change occurs in the milk supplied by the mother. The chemical analyses and correlations had to do principally with protein and the morganic constituents, particularly calcium and phosphorus.

In respect to the relationship of the analyses of milk to those of the body of the suckling the summary by Abderhaldens is as follows "Freept as regards the composition of the human infant and human milk, we find by a comparison of the corresponding values that there is a striking agreement between the ash of the young animal and that of the milk In the case of human beings, however we do not find any Bunge explains this fact by the assumption that the ash content of milk has not only the task of building up tissue but also serves in the preparation of the exercta especially the urine. The more rapid the growth of the sucl ling the less apparent will be the influence of the latter function. It is, therefore in general not to be expected that the percentage of composition of the milk of the infant will agree so closely in the case of human beings as with animals such as dogs, rabbits, and guinea pigs, which require the mother a milk for but a short time after birth but are soon placed upon a diet of green fodder It is easy to see that a milk corresponding closely to the chemical composition of the young as regards the morganic constituents will be more suitable for animals which develop very rapidly, whereas with the Pecies which develop more slowly the building up of the separate tissues does not take place so uniformly and there are not so many changes tak ing place at the time when the growing organism changes to another source of nourishment ' (p 369)

The alleged correlation between the composition of milk in respect to protein, ash, calcium and phosphorus and the rate of growth of the suckling is shown in a table by Abdorhalden (Table I)

From the Department of Pediatrics, Yale University School of Medicine Presented in abstract before The American Pediatric Society Thirty-eighth Annual Meeting 1226.

TABLE I	
THE ABDERHALDEN	TABLE

	DAYS REQUIRED	100 PAR	TS BY WEIGH	T OF MILK	CONTAIN
SPECIES	TO DOUBLE BIRTH WEIGHT	ALBUMIN	VSH	LIME	PHOSPHORIC ACID
Man	180	16	02	0 0328	0 0473
Horse	60	20	04	$0\ 124$	0 131
Cow	47	3 5	0.7	0 160	0 197
Goat	22	3 67	0 7713	0 1974	0 2840
Sheep	15	4 88	0 8406	02453	0 2928
Pig	14	5 21	0 8071	02489	0 3078
Cat	91	7 00	1 02	_	_
Dog	9	7 44	1 3282	0.4545	0 5078
Rabbit	6	10 38	2 4998	0 8914	0 9967

On this table Abderhalden comments as follows 8 "It is to be assumed a prior; that an animal which develops rapidly will require more building material than one whose development is slower pare the time required by the suckling to double its weight at birth with the amounts of albumin and ash-perhaps the most essential constituents for the formation of the tissues-contained in 100 parts of milk, it is evident at a glance that the amount of these increases in proportion as the development of the animal is rapid" (p 404) fact that the milk of different species of animals varies greatly is of The composition of the milk evidently has an effect much significance upon the rate of development of the suckling It is natural to expect that the nicher the milk is in its organic and morganic constituents, the more rapidly the suckling is able to build up its tissues If the milk of different species of animals all had the same composition, then the desired effect could be produced only by means of a much greater production of milk, and similarly a correspondingly greater quantity would have to be taken into the system of the suckling" (p 655)

That all biologists did not interpret these interesting data as Abder halden did is shown by the following quotation from Professor C S Minot's book on "The Problem of Age, Growth and Death" "This looks at first sight as if there were a relation between the composition of the milk and the period of growth of the animal, but you know very well that if you take the milk of a cow, which is very much richer in proteid material, and feed it to a baby, a human baby, that baby does not grow at the same rate as the young cow, but grows at the human rate. It is obvious, therefore, that it is somewhat more complicated than a mere question of food supply. We have here in fact one of the beautiful illustrations of the teleological mechanism of the body. These various species have their characteristic rates of growth, and by an exquisite adaptation, the composition of the mother's milk has become such that it supplies the young of the species each with the proper quantum of

protein material which is needed for the rate of growth that the young offspring is capable of . It is a beautiful adjustment, but there is not a causal relation between the proteid matter of the mother's milk and the rate of growth of the young. It is an example of correlation not of causation."

The Abderhalden Table is reproduced with varying degrees of consideration in many standard treatises dealing from one approach or another, with nutrition. One may cite as examples the textbooks of (zerny and Keller 10 Finkelstein 11 Pfaundler and Schlossmann 1 Heubner, 12 Langstein and Nassau 14 Lusk 15 Sherman 16 Starling 17 Hammarstei, 18 and Marfan 1

As the result of a study by the author in 1925 entitled Comparison and Interpretation on a Caloric Basis of the Wilk Mixtures Used in In fant Feeding " it seemed pertinent to apply the same method of evalua tion to the data of the Bunge Abderhalden Pröscher investigations A few quotations from this paper will give background and the method of The formulas of the food mixtures used in infant feeding are ordinarily expressed as the proportions by weight or volume which the various food components are of the total mass of the food-the so called percentage system. So formulated certain similarities and differences in foods may be suggested in a vague way but the essential fact inherent in the percentage system namely that the values of the nutrients are ratios which express only degree of concentration is often lost sight of For comparative purposes especially, it is difficult to perceive significant facts from small often fractional, percentage values of protein carbohydrate and fat which shift with changes in volume More helpful data would be apparent if water were disre garded and the food constituents were expressed as proportions of the solids in the mixture Protein, carbohydrate fat and salts would then be shown as they are related to each other independent of their relation to the diluent '

'Although it is possible to establish a satisfactory means of comparative study of various foods on a quantitative basis it is advisable to go further to a more fundamental unit for a common currency in infant feeding. The calorie is the unit used everywhere by physiologists in the investigation of problems of nutrition. Itself a measure of energy the calorie is used constantly in metabolism studies. As a physiologic unit, the colorie is greatly superior to the gram as the unit to which the protein carbohydrate and fat food components may be reduced. The calorie is a least common denominator of all energy yielding food constituents and their derivatives.' Briefly stated, in the analyses and comparisons of milk mixtures described in this paper the total caloric value of a given amount of the food as fed is estimated and the percentage relationships which exist between the total calories and the

calonies of protein, of carbohydrate and of fat are then determined Thus, the energy-yielding components are expressed and compared without confusing alliances with volumetric data "

"In regard to the salt content of infant feeding mixtures, it may be stated that in general the mineral constituents of most of them parallel the milk content. When milk is diluted with water and the requisite calories of a milk mixture are made up with salt-poor food components, the actual mineral intake is greatly reduced. The salt content of milk mixtures may be so expressed to bring out its relationship to the total energy value of the food or to that of any one of the food components." For example, in human milk—on the basis that 100 c c contain 200 mg of inorganic salts and have an energy value of 64 calories of which 46 are supplied by protein—there are 31 mg of ash for every calorie of milk and 43 mg for every calorie of protein. The individual electrolytes may be similarly treated.

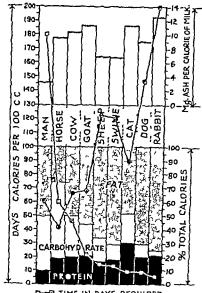
#### DATA

In Table II A I have added to the Abderhalden Table (leaving out the data on calcium and phosphorus) the figures for lactose and fat which were given in the original analyses on which the table was based 2, 3 4 5, 6 Then in Table II B, I have set down computations of the calories per 100 c c of milk, the percentage of these calories in protein, carbohydrate and fat and the milligrams of ash per calorie of milk. These data are graphically shown on Chart 1

In Table III I have set down data corresponding to those set forth in Table II but concerned only with milks used in human dietary in one country or another \* These data are shown graphically in Chart 2 Similarly, in Table IV, are set forth data concerning the milks of animals rarely studied. It should be pointed out that in Tables I, II and IV there are analyses of milks which because of the inherent difficulties in sampling may well be inaccurate as indicative of the composition of the average mature milk of the species. It was for this reason that Table III was developed with the thought that the analyses there given were concerned with milks more or less extensively used in certain localities and samples were, therefore, available which are truly representative of the mature milk of the species

In Table V are data showing the rate of growth of the female young of various breeds of dairy cattle and the composition of the milks of the breeds. In addition, the calories per 100 c c of milk have been computed and also the percentage of these calories in protein, lactose and fat

The studies of the ash of various milks are set forth in Tables VI, VII and VIII. In Table VI, the Bunge Abderhalden Proscher data are set forth in respect to the milligrams of ash per calorie of milk and per calorie of protein, also the relation of "lime" and "phosphoric acid" to calories of protein. In Table VII are set forth for those milks enumerated in Table III, the relationship of total ash and of six of the most important constituents, quantitatively speaking, to calories of milk. Table VIII gives the data with respect to the same milks of the relation ships of the total ash and of the same six constituents of the ash to calories of protein.



TO DOUBLE BIRTH WEIGHT

Chart 1—Based on data in Table II Graphs show caloric value per 100 a.c. of milk of species shown in Abderhalden Table and percentage of calories in protein carbohydrate and fat also, milligrams of ash per calorie and days required by suck lings to double birth weight.

TABLE II
THE ABBERHALDER TABLE WITH ADDITIONAL DATA AND COMPUTATIONS

		1						В		
SPECIES.	DAYS RE QUIRED TO DOUBLE	PKR	OENT C	r solii	D8 1M	ORUE: ORUE:		ent of Lories		Md ASH PER CALORIE
	BIETH WEIGHT	PROT	CARD.	PAT	ASE	100 a.a.	PROT	CARB	PAT	OF MILK
Man	180	16	61	34	0 20	61	10	40	50	82
Horac	00	20	57	12	040	42	10	55	26	9.5
Cow	47	8.5	4.0	87	070	67	20	20	150	104
Goat	22	3 67	3 61	4.88	077	80	21	( 22 -	57	11.3
Sheep	15	4.88	5 04	9.29	0.84	128	17	17	66	6.5
Pla	14	5 21	88	0.54	0.80	120	18	11	71	67
Cat	91	7 00	478	4.75	102	90	30	22	48	11.8
Dog	9.	744	8.84	11.62	1.82	147	20	9	71	90
Rabblt	( 8 '	10.88	198	1671	248	200	21	4	75	12.5

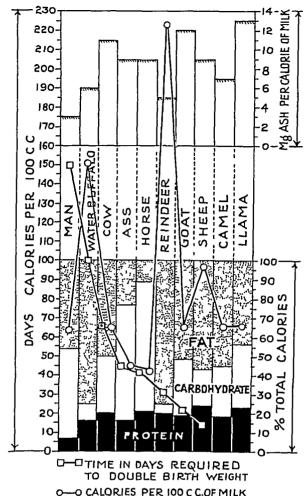


Chart 2—Based on data in Table III Graphs show caloric value per 100 c.c. of milk used in human dietary and percentage of calories in protein carbohydrate and fat also milligrams of ash per calorie and days required by sucklings to double birth weight.

Table III

A New Table Based on Data from the Literature and from Personal Communications These Data Have to Do Only with Milks

		_	USE	) IN IN	FANT I	EEDING	<del>-</del>			
SPECIES	DAYS RE QUIRED TO DOUBLE	PER	CENT C	F 50111	)S I	CAL ORIES PER	1	ENT OF LORIES		MG ASH PER CALORIE
	BIRTH WEIGHT	PROT	CARB	FAT	ASH	100 CC	PROT	CARB	FIT	OF MILL
Man	150	1 15	7 5	3 26	0.2	64	7	47	46	3
Water	100	6 03	374	12 46	0 89	151	16	9	75	6
Buffalo Cow Ass Horse Reindeer	66 76 45 60 42 31 22	3 28 1 82 2 2 11 1 3 18	4 84 6 86 6 97 2 7 4 62	3 61 1 13 0 54 18 7 3 79	0 72 0 42 0 41 1 2 0 79	65 45 42 223 65	20 16 21 20 19	30 61 68 5	50 23 11 75 52	11 9 9 5 12
Goat	14	5 83	4.72	6 12	0.89	97	24	19	57	9
Sheep Camel	9	2 92	4 58	41	05	66	18 23	27 34	55 43	7 13
Llama	9	39	56	3 15	08	66	40	34	40	10

True TV

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875.7188	DAYS REQUESTS TO DOUBLE		ER CENT OF	TER CENT OF SOLIDS IN		CALORIES	PER	PER CENT OF TOTAL	orte.	MO ABII PER MO ASII PER OALORIE CALORIE	MO ASII PER
	BIEFIL WENDER	PROT	CARB.	TAT.	TLEY	100 ca {	TOTE	GARR.	TAT	OF MILK	VERTORY TO
Aufnen 19g	194-14	50 ar	_ 16 av	7 17 00.	21.0	5.6	2	=	69	2	82
Plg	7 30	0.08	5.21	699	10	103	Ę	0;	ž.		3 5
Elephants	-	8 40	7.18	20.58		6	=	35	2		2 5
Elephants	-	197	8.59	9 10		¥	or	- ! !:		} =	; 5
Elephant		3-31	7.39	33 07		15		; ;	3	-	2 5
Zebu	-	1.03		4			, a	: :	3	10	
Blue Whale	_	13.45		30.0				15	56	51	2 2
Bartenwhale	•	943		197		15	2 0	3	28	•	2 8
Monkey (Mangabey)	-	25	10	-4		18	2		, c	9 6	3 5
For	10	2	_	6.3		200	, .		16	10	0 6
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TABLE V

DATA CONCERNING THE COMPOSITION OF MILK AND RATE OF GROWTH OF VARIOUS

BREEDS OF DAIRY COW

BREED OF	DAYS RE QUIRED TO DOUBLE BIRTH	PER	CENT O	r solii	os in	CALORIES PER 100 C C		ENT OF LORIES	
	WEIGHT	PROT	CARB	FAT	ASH	OF MILK	PROT	OARB	FAT
Holstein	76	3 1	4 6	3 4	0 68	62	20	30	50
Shorthorn	73	33	48	36	0.73	65	20	30	50
Ayrshire	69	33	50	38	0 69	68	20	29	51
Jersey	66	38	50	51	0.75	81	18	25	57
Guernsey	- <u> </u>	38	49	49	0 75	80	20	25	55

TABLE VI

THE RELATIONSHIP OF TOTAL ASH TO CALORIES OF MILK AND OF TOTAL ASH, "LIME" AND "PHOSPHORIC ACID" TO CALORIES OF PROTEIN ACCORDING TO

BUNGE PROSCHER ABERHALDEN DATA

SPECIES	CAL, PER 100 C C OF MILK	MG ASH PER CALORIE OF MILK	CAI OF PROTEIN PER 100 C C OF MILK	MG OF ASH PER CALORIE OF PROTEIN	MG OF LIME PER CALORIE OF PROTEIN	MG OF PHOS ACID PER CALORIE OF PROTEIN
Man	61	3 2	6 4	33	5	$-\frac{7}{7}$
Horse	42	95	8.0	50	15	16
Cow	67	104	14 0	50	11	14
Goat	68	11 3	14 68	51	13	19
Sheep	123	68	19 52	42	13	15
Pig	120	67	20 84	38	12	14
$\overline{\mathtt{Cat}}$	90	11 3	28 0	36		
$\mathbf{Dog}$	147	90	29 76	44	15	17
Rabbit	200	12 5	41 52	60	21	24

TABLE VII

THE RELATIONSHIP OF THE TOTAL ASH AND SOME OF ITS CONSTITUENT ELECTROLYTES TO CALORIES OF THOSE MILLS TABULATED IN TABLE III

	CAL PER		7	IG PER C	ALORIE O	F MILK C	)F	
SPECIES	OF MILK	TOTAL ASH	К,0	NA <sub>2</sub> O	CAO	MGO	P205	CL
Man	64	3	0 95	0 20	0 72	0 11	0 54	0 56
Water Buffalo	151	6	086	0 36	20	0 18	20	0 44
Cow	65	11	2.75	0 78	26	0 31	2 92	152
Ass	45	9	23	0 38	2 89	0 20	2 65	1 09
Horse	42	9	245	0 33	2 93	0 29	31	0 73
Reindeer	223	5	0 79	0 87	1 36	0 14	1 64	0 22
Goat	65	12	20	0 95	3 03	0 24	4 37	1 55
Sheep	97	9	2 22	0 40	2 85	0 13	2 77	0.7
Camel	66	7	14	0 27	2 04	0 21	2 29	1 16

## ANALYSIS OF DATA

Despite possible inaccuracies in certain data there is one finding of striking constancy in the analyses as tabulated, namely, most milks have about 20 per cent of the total calories in protein. There are exceptions but the only one which is certain is human milk which has less than 10 per cent of its total calories in protein. It would seem from Table IV that in this respect the milk of the elephant is very much like human

TABLE VIII

THE RELATIONSHIP OF THE TOTAL ASH AND SOME OF ITS CONSTITUENT ELECTROLYTES
TO CALORIES OF PROTEIN OF THOSE MILKS TABULATED IN TABLE HI

======================================	CAL OF PROTEIN		סוג	PFR CAI	ORIF OF	PROTEIN	or	
SPECIES	C.C. OF MILK	TOTAL ASII	K,0	<b>አ</b> ሌ0	CYO	ngo	r <sub>t</sub> o,	CL
Man	4 60	43	13	28	0.0	16	7.5	7.0
Water Buffalo	24.12	37	5.4	23	12 5	10	12 4	27
Cow	13.12	55	13 6	3,0	12.9	1.5	14 5	7.4
λm	7.29	58	140	2.3	178	1.2	163	67
Horse .	8.8	46	117	10	140	14	14 9	15
Reindeer	44.4	27	3.0	4.4	0.8	0.78	8.2	11
Goat	12.72	60	10.2	4.9	15.6	12	220	8.0
Bheep	23,32	38	0.3	1 69	11.9	0.55	116	2.0
Camel	11 68	43	79	1.5	11.5	2.1	12.9	61

The sources of the data on which Tables III IV VIII and VIII are based will be found following the summary

milk. In this Table I have set forth three analyses of elephant's milk although there are variations, chiefly in the amounts of fat, nevertheless the percentage of total calories in protein in all three calculations is be low ten. The striking fact rumains that in analyses the essential accuracy of which in all respects one has little reason to question human milk stands apart from that of all other species examined in respect to the percentage of total calories in protein

Out of these observations comes another namely that there is no correlation between the rate of growth of the suckling and the protein calorie relationship. Indeed if there is any correlation in this domain at all it is closer between rapidity of growth and the calorie concentration of the whole milk than between any other two variables in the data. But this correlation while suggestively close in Table II and Chart 1 is vitiated when one studies the data in Table III and Chart 2. For example, the reindeer calf doubles its birth weight in one third the time required by the water buffalo calf, but the mother of each suckling supplies milk of yery high calorie value.

In all of these matters the factors of maturity of the suckling, total caloric requirement and quantity of milk taken per diem must be kept in mind. Climate seems to play no rôle when one observes, in the example of the reindeer and water buffalo just cited that one animal is arctic in its habitat and the other tropical. Within the species itself there are considerable variations in composition of milk and in rapidity of growth One has but to observe the variations in the composition of the milk of different breeds of dairy cows and the different rates of which the female calves of such cows grow (Table V)

One might also call attention to the type of hody covering of the different animals under consideration. In some the skin is bare, in others covered by hair and in others, by wool. The cystine content of

some samples of hair is high, but the milks showing a high percentage of the total calories in protein are those in which, for the most part, casein is the predominant milk protein and casein is low in cystine \*

Apparently there is no correlation between the protein-total caloric relationship and the quality of the protein so far as albumin and casein content is concerned. In the milks of the species listed in Table III (no data for llama) casein is greatly in excess of albumin excepting in that of man and ass 25

It would be of great biological interest if a study of the milks of the various primates could be made along the lines here suggested. If some of the milks showed the protein total caloric configuration characteristic of human milk, while others showed the pattern so characteristic of all the other milks here studied, the matter might have phylogenetic significance. In Table IV I have given the only analysis of the milk of a primate (Mangaber) of which I have knowledge. Eighteen per cent of the calories are in protein

When one turns from a consideration of protein to that of the relation of the ash and of its individual constituents to the total calories (Tables VI and VII) one finds little correlation of these data with rate of growth If the ash is expressed as milligrams per caloric of milk, the ash of human milk is lower than that of any other of the animals studied If one expresses the total ash as milligrams per calorie of protein (Tables VI and VIII), there is, perhaps, less extreme variation excepts the data concerning reindeer milk, the range of variation be tween the lowest (37) and highest (60) values is 23, this, of course, does not approach so nearly a constant in the ash-calorie correlation as is indicated above to be true of the protein-caloric relationship studies the ash-calone relationship of each of the individual electrolytes of the total ash (Tables VI, VII and VIII), no constancy for the values for each species in relation either to calonies of milk or to calonies of protein is obvious. In general, one would expect and does find a more constant correlation between ash and protein calonies than between ash and total milk calories. It is possible, however, that the electrolytes are more closely related to protein itself than to nutritional requirements

<sup>\*</sup>The body coverings of the animals discussed in this paper are a matter of common knowledge with the possible exception of facts concerning water buffaloes and elephants

Concerning the water buffalo C O Levine<sup>20</sup> writes as follows. The mature animal has very little hair on its body. The sides back and thighs of the animal are almost bare of hair. The shoulders and knees have the most hair where it is about 2 to 3 inches long. The buffalo calves are born with a rather heavy coat of long rather soft, dark hali all over the body which gradually disappears after one year of age is reached and is replaced by shorter and coarser hair thinly distributed over the body.

Concerning the elephant, G H Evans<sup>21</sup> writes as follows. The hairs are bristin character stiff to the touch and firmly rooted and are more abundant in certain localities. In the adult they are numerous on the forehead lower lip upper lip orlices and the ears and end of the tail. On the latter they are larger and stiffer in character and grow from the anterior and posterior borders and tip extending much higher up on the anterior where they are usually longer. Young elephants usually have much more hair about them than adults.

One may perhaps emphasize the point that in respect to paucity of hair the infant and baby elephant are as closely related as the milks of their mothers seem to be in protein-total calorie proportions

as such. It is only suggested then, that while the ash of human milk is very low in relation to total energy value the figures expressing the relationship of ash to protein energy for the milk studied all though not constant, are strikingly near the same order of magnitude

In contrast to the constancy exhibited by the protein fraction of the total energy value of the milks studied (that of the human being excepted) the proportions in sugar and fat show the most extreme variations from the very high fat and low sugar of reindeer and water buffalo milk to the low fat and high sugar of the milk of the ass and of the horse

Likewise there are wide variations in the water content of these milks is shown by the extreme fluctuations in the calorie value per 100 c.c.

#### OFNIRAL COMMENT

The primary nutritional requirement of the organism is energy. It seems to the author that although the biological significance of the data submitted in this paper is obscure the facts may be linked with some of the so-called "laws" of energy metabolism.

Rubner formulated the law that includes in a proportional to the superficial area of the animal. Even with variation associated with species degree of maturity growth size and sex, it is remarkable how narrow is the range through which this proportion moves. Man apparently, is not an exception to this law.

'Rubner finds in all species the constant retention of approximately the same percentage of the energy ingested which averages 34.4 per cent, except in the east of man, in whom the energy retained for growth is only 5.2 per cent. (Laisk 15 p. 571)

Furthermore, Rubuer formulated a law of constant energy expenditure" as follows The amount of energy (calories) which is necessary to double the weight of the newborn of all species (except man) is the same per kilogram no matter whether the animal grows quickly or slowly '(Lusk, p 567)

To these formulations none of which of course are mathematically rigid may be added from this study the statement that instead of the rate of growth of the suckling being correlated with the amount of protein and salts in the mother's milk the facts seem to be (1) that for many sucklings infants excepted the proportion of the total energy intake in protein is the same for all species (20 per cent) when the sole source of food is the mother's milk and (2) that the inorganic salts in relation either to the milk or protein calories while not constant, shows no correlation whatever with the rate of growth of the young

One may ask to what extent a prolonged period of immaturity in the infant enters as a factor in this matter. Certainly, under natural conditions, the young of all the animals studied receive other food than the

<sup>&</sup>quot;I refer of course, only to the sucklings of those species of animals studied in this paper in whom acceptable analyses of milk are available.

mother's milk at an earlier age than does the infant. The question raised cannot be answered here, but I should like to call attention to the interesting chart of Brody<sup>28</sup> (Chart 3, Lusk,<sup>15</sup> p 570), which shows a remarkably constant pattern for the growth curve of a number of animals, but when the growth curve of man is plotted on the same basis the exceptional nature of the human curve is brought out. However, this eccentricity of the human curve is evident only for the long period prior to puberty. This exceedingly long period of development for the human young between birth and puberty seems to have laws peculiar to itself

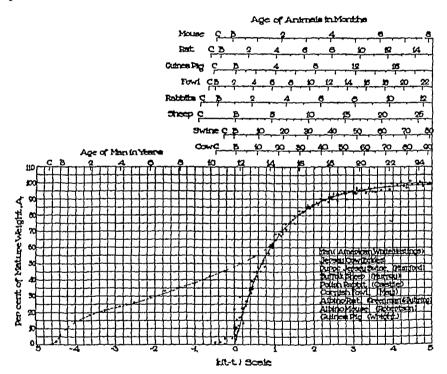


Chart 3—Age of animals in months—The growth curves of all domestic animals have the same shape and there are no graduations between man and animals. It is extremely desirable to determine the position of growth curves of primates other than man with respect to man on one hand and other animals on the other. The upper axes represent ages in absolute units (months for animals and years for man). O represents conception and B, birth. The numerals on the lower axis represent relative units (Brody)

Whatever may be the biological significance of the constancy which the protein fraction of the total energy value of the milks of many species of animals exhibits, the fact that human milk is a striking exception may be a phenomenon associated with what Professor Lusk called "the biological distinction of the protoplasm of the growing human being, which separates it from that of the lower mammals" (Lusk, 5 p. 572)

#### SUMMARY

The data of Abderhalden showing an alleged correlation between the rate of growth of sucklings and the protein and ash of the milk of the species have been analyzed from the standpoint of the percentage of the total calories in protein, carbohydrates and fat, also, attention is called to the relationship of the ash and some of its constituent salts to calories of milk and of protein

Additional data, similar to those of Abderhalden have been analyzed in the manner just indicated

According to the method of evaluation set up in this paper there is no correlation between the rate of growth of the suckling and other factors presented in the Abderhalden Table and in additional data

With the striking exception of human milk, the percentage of the total calories in protein is uniformly close to twenty for the milks of a number of species of animals

In human milk, by contrast, the percentage of the total calories in protein is less than ten

The biological or other significance of these facts is obscure Because of possible phylogenetic implications the milk of other animals—primates in particular—should be studied in the manner indicated in this paper

Sources or Data in Tables III, IV, V, VII and VIII

Mas

Composition of Milk Holt et al., 22.

ll'ater Buffalo

Composition of Milk Levine C. O., 20

Composition of Ash of Milk König, 23, p 06.

Rate of Growth Data supplied by Mr To Shue Tsol of the Department of Animal Husbandry Canton Christian College, Canton, China, through Dr William W Cadbury personal communication, October 15 1925 The work was carried on under the direction of Mr C O Levine

CALT NO.	BIRTH WEIGHT	SUBSEQUENT WEIGHTS	DAYS REQUIRED TO DOUBLE BIETH WEIGHT
3	63 lb	181 lb on 130 day	120
4	85 Ib	170 lb on 145 day	145
_	76 Ib	152 lb on 112 day	112
6	60 lb-	122 lb on 181 day	131
8	··	140 lb on 75 day	75
10	71 lb	140 lb on 77 day	60
11	60 lb		100
Indian Buffalo Cali	85 lb	190 lb on 120 day	100

Estimated by means of straight-line graphs.

Dr Cadbury's communication states 'All calves were removed from their mothers at birth and milk was milked from the mother and fed to them for the first month at the rate of one pound of whole milk to 10 lb of body weight of the calf for the first month. After this first month one-half pound of whole

milk and one half pound of soy bean curd, mixed, were fed to the calves for ten days. Then one third whole milk and two thirds soy bean with some bran added were fed for ten days. Finally a total of one pound of milk daily and bran bean constituted the calves' food "

Cow

Composition of Herd Milk Konig, 24, p 219

Composition of Ash of Milk Holt, et al., 22

Composition of Milk of Special Dairy Breeds Rogers, 25

Rate of Growth Eckles, C. H., Chief, Division of Dairy Husbandry, University of Minnesota, 26, and personal communication June 23, 1925

488

Composition of Milk Konig, 24, p 394

Composition of Ash of Milk, Konig, 24, p 394

Rate of Growth Through the kindness of Professor Marfan I received the following data from M Barrier of Alfort, France

Average weight of ass at birth

Small African race-15 K

Small race from south of France-30 K

I arge race (Portou)-25 K.

This weight is doubled in from 45 to 60 days

In a personal communication, Dr Sidney Kaliski of San Antonio, Texas, states that a "leading veterinarian" informed him that the burro doubles its birth weight in 6 weeks

Horse

Composition of Milk Konig, 24, p 393

Composition of Ash of Milk Konig, 23, p 663

Rate of Growth Mr H H Reese, Animal Husbandry Division, U S Dept of Agriculture informs me from actual observation on a Morgan colt that the birth weight was doubled in 42 days

Reindeer

Composition of Milk 11ppo, A, 27

Composition of Ash of Milk Konig, 24, p 395

Rate of Growth

OBSERVATION	BIRTH WEIGHT	BIRTH WEIGHT DOUBLED IN
1	35 to 4 Kg	35 days
2	40 to 5 Kg	38 days
3	40 to 5 Kg	28 to 35 days
	Average	31 days

This information was secured by Professor E A Park, Nov 30, 1925, through the kindness of Mrs Carl Bassoe of Norway, from Messrs Kristian Nissen and Arne Arnesen of the Inspektoren for Rendriften, Oslo, Norway

Goat

Composition of Milk Konig, 23, p 351

Composition of Ash of Milk Abderhalden, 6, p 457, 458

Rate of Growth In personal communication, October 7, 1924, Professor Pierre A Fish, or Department of Veterinary Physiology, New York State Veterinary College, Ithaca, N Y, informed me as follows concerning two kids (sisters) "of a breed partly Sanneen"

віктн weight 20 Kg	BIRTH WEIGHT DOUBLED IN 20 days
1.7 Kg	23 days
Average	22 days

Sheep

Composition of Milk König \_4, p 376

Composition of Ash of Milk König, 23 p 660

Rate of Growth In a personal communication July 7 1024 Mr D A Spencer of the Animal Husbandry Division of the U S Department of Agriculture in forms me that sheet double their birth weight in about 14 days.

For

All data from Young and Grant, 29 p 805

Camel

Composition of Milk In a personal communication, June 14, 1020 Lt Col McCarrison of the Pasteur Institute Cooncor, S India, gave me two analyses of the milk of the earnel These analyses were made by Dr P L. Lander, Agricultural Chemist to the Government of the Punjab I have taken the average since the analyses were nearly the same

Composition of the Ash of Milk König 23 p 662.

Llama

Composition of Milk König 23 p 661

Cuinca Pig

Composition of Milk and Rate of Growth Abderhalden, 6 p 437 458

Composition of Wilk

- (a) Künig 23 p 604
- (b) Heineman 28 p 70
- (c) Doremus 20, p 486

7cb≠

Composition of Milk König 23 p 661

Blue Whale (Balachopera Sibbaldi)

Composition of Milk König 24 p 400

Bartenichale (Family Balaeniden)

Composition of Milk König 24 p 400

Monkey (Mangabey)

The author is fortunate in being courteously permitted to use some proliminary observations of Dr Gertrude van Wagenen (Department of Obstetries and Gynecology) and Dr Harold E. Himwich (Department of Physiology) of Vale University Ten samyles of milk were obtained each sample amounted to a cubic centimeter and was a complete milking Some samples were used for the protein determination and others for enrichelydrate fat and ash respectively. The data in the table are averages of at least two analyses.

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# THE TREATMENT OF POLION) ELITIS PAST AND PRESENT

## JOHN RUHRAH, M.D. BALTIMORF, MD

THE question of the treatment of poliomyclitis resolves itself into two parts, one the specific treatment by serum or other means as yet unknown, the other the management of the end results of the lesions in the nervous system

The specific treatment may be said to date from 1910 when Netter. Gendron and Touraine used convalescent serum. Various other serums have been suggested and used, such as normal horse serum, pneumococ cus scrum and the like and scrums prepared in horses or other animals using streptococci, as the serum of Rosenow reported on first in 1917 Animals have also been immunized to material taken from monkeys paralyzed by poliomyelitis by Neustädter and Banshaf, Pettit, Weyer. Park and Banshaf, Fairbrother, and Fairbrother and Morgan. recently serum from adults has been used The results vary who have used the serums most are inclined to believe that the serum from patients who have been left with residual paralysis has a definite, if weak, power of preventing or limiting the paralysis if given in the preparalytic stage Others, also basing their judgment on experience, are sceptical as to its value. As yet no satisfactory large sories of cases treated with a like series of control cases has been reported. have been some series of cases treated and controls reported but these for one reason or another are open to criticism. The question of the value must be regarded as an open one. It seems to be on a theoretically sound basis, and from such studies as Machamara's it would seem pos sible to prepare a serum which if administered sufficiently early in large enough quantities would give as good results as she has obtained.

About the management of patients who have had the disease there has been and still is a considerable difference of opinion. John Hunter niggested the value of the exercise of the will in training muscles that had been paralyzed but not in regard to poliomy elitis although he records at least one case which he had observed. Underwood and the physicians who shortly followed him made no therapeutic suggestions of value beyond the use of 'irons to the legs' and Samuel Merriman, who edited one of the later editions of Underwood's book, said, "It may be doubted whether irons to the legs can ever be useful in a state of paralysis of the lower extremities. If the limbs are paralytic, how are irons to the legs to enable the patients to walk?" This was two years after John Shaw had written his interesting book "On the nature and treatment of the directions to which the spine and the bones of the chest are subject." Shaw

used methods of stretching and exercises not unlike some methods emploved today and some of his cases were undoubtedly of poliomyelitic origin W J Little used tenotomy and manipulations, and many of his cases were due to poliomyelitis Had he had the sharp eye and understanding brain of Jacob Heine he would have made a name for himself m infantile paralysis as well as in Little's disease Jacob Heme, m 1840, in his Beobachthtungen über Lahmungzustande der unteren Extremitaten und deren Behandlung laid the firm foundations of the coirection of paralytic deformities by the use of apparatus, exercise and strengthening the entire body. He used warm baths and steam baths before manipulation, and when he could not get 11d of the contractions he used tenotomy which had been suggested by Delpech in 1823 and perfected by Strohmever a little later. Heme also used exercises for the muscles and devised machines to help the patient and figures one of these machines in his plates. His orthopedic apparatus is the same in principle as that used today and very much the same in execution 1860, in a second edition of his book, he called attention to the possibility of preventing deformity by suitable apparatus. Eulenberg in 1859 made a table of the deformities and the muscles which were paralvzed and those which were antagonistic, with a view to exercise, and Ling in Sweden developed his system of so-called Swedish exercises or Heilgymnastik The latter spread rapidly over the world The Hungarian, Matthias Roth, one of Ling's students, introduced the system into England, and Charles Favette Taylor brought it to America almost everywhere physicians and surgeons, much as they often do now, used only one part of the therapeutic armamentarium, Ling his exercises, Roth various methods including apparatus for support, many of the orthopedic surgeons depended on apparatus or operations or both to gether and neglected exercise Duchenne of Boulogne about 1850 began to develop the use of electricity, about which he was more enthusiastic than any one of his time or after. He also used apparatus of great ingenuity for replacing of supporting paralyzed muscles Moritz Meyer was another great exponent of the use of electricity

The greatest genius among those dealing with infantile paralysis in those days, and, indeed, no one has surpassed him, was Charles Favette Taylor, founder of the New York Orthopedic Dispensary and Hospital He early became interested in the protection of bones and then of muscles. In 1867 he published a little book of 119 small pages which is without doubt one of the great American medical classics, a book of such larity that few libraries have a copy. It is a book evidently not appreciated fully in its own day and now practically unknown but one which contains all the principles of the proper management of a case of poliomyelitis as far as the care of the apparatus of locomotion and station is concerned. The principles of treatment as laid down by him have been in part used by others, but for the most part they are just

being rediscovered today. Some little of his work has found its way into midical and surgical textbooks for the most part writers from his time on have failed to stress the essential points. Seelignuiller, in Gerhardt Handbuch der Linderl rankheiten in 1850, outlined the therapy in a masterly way omitting however some points of great importance. In the recuperative stage he advised among other things electricity mas sage given to the paralyzed muscles, heat spray and steam douches, warm baths, hydrotherapy, and in the chronic stage electricity, massage exercise hydrotherapy and the like together with apparatus and such helps as crutches walkers and exercising machines. He mentions the use of apparatus to prevent deformities and contractures but does not stress this point sufficiently.

Wharton Sinkler in the otherwise excellent article in Keating's Cy clopedia of Disease of Children in 1890 advised electricity and mas sage and the use of the infected parts and urged that the child be made to walk as soon as possible. He makes no especial mention of the use of apparatus to prevent deformity but suggests its use after it has occurred.

From that time on but few spoke and when they did it was like the voice of one crying in the wilderness. We may mention Hugh Owen Thomas and Sir Robert Jones who insisted on the correct methods and Colin Mackenzie, too taught muscle reeducation and muscle protec tion but otherwise the therapy of poliomyelitis seemed at a standstill except that the orthopedic surgeons were able to do more and better op erations for the correction of deformities but their prevention was not stressed by many and as a rule the patients were not given sufficient rest and were allowed to walk too soon. In 1917 Lovett1 published his observations on 1836 cases and showed that weight bearing in the first vear, where trunk and legs are involved is risky and advised ambulatory exercise only when complete recovery has occurred or when there is reason to believe that hope of complete recovery or further substantial gain must be abandoned. It might be added that this is to be based on frequent examinations of the muscles and not any time factor. In a re cent article on Physical Therapy in Infantile Paralysis," the author states, 'In any case after six or seven months it is generally advisable to allow getting up on the feet for the effect of the general condition and morale even though the length of time daily may be restricted Cases which have not responded to treatment should be started walking for the same reason This statement is calculated to do very consid erable harm to many patients—as noted below. The writer be it said to his sinful sorrow has been guilty of misleading statements on this point which he has since learned from experience are wrong. The lack of exact statement in most textbooks and indeed in many articles is rather remarkable in view of the amount of recent study of the subject

Let us look for a moment at the work of Taylor and note how completely he covered the ground as far as principles of treatment are con-His views as to the pathologic conditions may be disregarded, since little was known in his day. He noted, as did Heine, that all cases tend toward recovery "Very few cases are to be met with where some portions of the originally paralyzed members have not entirely recovered " He questioned why more patients did not show greater recovery when the tendency was that way and came to the conclusion "that it is not always because Nature has wholly exhausted herself, but because accidental circumstances have come to interfere with her work, which would otherwise have gone on much further " He noted the contractures of the muscles and the deformities and said "I reply, without hesitation, that contractions and distortions are not necessary consequences of this paralysis, that these unhappy results are always and entirely preventable Indeed, what seem to be contractions of certain muscles-generally flexors-are not contractions at all, but simply a mechanical shortening of the muscles when their attachments are for a length of time brought closely together But in infantile paralysis, the shortening of certain muscles is not the first or principal damage done by improper and careless positions of the paralyzed limbs The shortening, though the most noticeable, is not the first or worst complication which arises to arrest the progress of improvement and to set in train a series of conditions favoring the formation of distortions and deformities Any position of a limb which allows the extensor muscles to become shortened must inflict a worse damage on the flexors by keeping them extended till they lose their remaining iiritability and become degenerated Now, we have another fact connected with these cases when they have arrived at the stage of deformity, viz, this difficulty of treatment consists much less in relaxing the shortened muscles than in giving tone and strength to their antagonists—the lengthened and weakened ones Indeed, it is this, in the destruction of all remaining irritability, and in many instances the destruction and entire loss of the substance itself of the expanded muscle, which constitutes the principal anxiety in treating this class of deformities this important consideration has been many times neglected, if not entirely lost sight of, let us consider the effect of simple extension upon the power and function of muscular tissue in its healthy state "

He goes on to point out that "To retain a healthy muscle in an expanded state for a certain length of time is to diminish or destroy its irritability and contractile force. To extend a muscle while in the act of contracting, that is, to overcome it, is to, at once, destroy its irritability and force" He uses as illustration the stretching of the sphincter and as is frequently done for the relief of fissures, etc.

The mechanics of the production of deformities through the imbalance of muscles and weight bearing too early is clearly set forth and by

proper care the deformities are always preventable. "If the feeble muscles and ligaments of the joints were not subjected to overwhelming strain, by baring too early an injudicious weight, they would not give way under the first attempt at exercise, instead of being strengthened by it—which they might be, if proper precaution were observed. The treatment of infantile paralysis in the early stages consists for the most part, in noninterference with the recuperative efforts of Nature. We are to remember how little it may take to injure the enfeebled muscular tissue and diligently guard the patient from possible harm—knowing the direction from which injury is most likely to come."

The recuperative period is a very critical period, and it is difficult to know when to exercise the muscle and how much. If it is not used it will waste from nonuse, and if too much is given it will be destroyed by overuse. "Evidently, then, we must contrive to afford the muscles to act within their capacity-alike avoiding mactivity or overactionuntil their development has reached the point where they are capable of being made available in sustaining the weight of the body in loco-We must furnish the muscle an exercise that shall not exceed its capacity And not until the powers of the muscles have been developed till they are equal to sustaining the weight of the body should they be required to sustain it. There is no physiological prin ciple more clear or simple. The leg of a paralyzed child in relation to its body may be compared to those of an infant called upon to support the trunk of a man, they cannot do it, and should not be allowed to attempt it till they have grown equal to their load. But every particle of latent force calls for use, action is its life and growth and under these unusual circumstances we are called upon to furnish the oppor tunity for whatever force there is to act

"If the patient has been carefully attended, so that no damage is done by faulty positions while in a state of muscular atony there will be no difference in the rate of recovery, nor will there be shortening or lengthening of different muscles and the patient can begin to stand and walk at a much earlier stage, and with much less strength than when a very small amount of shortening has been allowed to take place. The reason for this is that the least contraction of the fiexor muscles will at once throw the patient out of his natural position and the weight of the body must be held entirely by the force of the muscles instead of resting on the bony framework, with only sufficient muscular aid to keep it great."

It will be seen that the principles of the treatment of poliomyelitis were laid down with great accuracy and clarity but with but few exceptions until recently these principles have been disregarded. C L. Lowman and Jean Macnamara in addition to those noted above may be mentioned among those who have striven to spread this gospel of the prevention of deformity and the protection of muscles which may be

accomplished by the early use of proper splints to hold the body and the limbs in line and at the same time to give relaxation to the paralyzed In all paralyzed patients the most important muscles should be favored first until their recovery is assured These are the deltoid. extensors of the wrist, the opponens of the thumb, the gluter, the quadriceps, the calf muscles, tibialis anticus and the abdominals. These must be placed at rest in a relaxed position, which is in recumbency in the same position the body would be if standing erect. Stretching of the muscle should not be allowed in handling the child as is so frequently done It must be remembered that in the early stage and as long as improvement is looked for, lest is the most important thing both general and local must be guarded against. When the time comes to start exercise, it should be begun with very little and always kept well within the capacity of the muscle Passive movements may be made when the movements are too much for the patient and the patient wills the movement at the same time. This is important for volitional movements are the ones which build up the muscle power Assistance must be given and support, as well, in making movements with weakened muscles As the power returns great care should be taken to exercise only the muscles which need it and to make such changes in the splint ing from time to time as may be needed by the change in balance of power due to improvement Great care must be taken to keep the body in line to permit of good posture when the time comes to stand

The nature of the splints will vary with the muscles involved. The modified double Thomas splint as suggested by Machamara<sup>2</sup> will be found useful, since this permits the patient to be kept in line with such adjustments as may be needed in the aims and legs. The abdominal muscles are looked after by a corset and the support extends from head to foot. Legs and aims that are affected should never be left to dangle even for a moment. Eternal vigilance is the price of the best recovery.

Muscle training is best carried out by a trained physiotherapist well grounded in anatomy and muscle function, but as this is impossible in most cases which must be treated at home, the simpler movements may be taught some member of the family and the treatment carried on under as close supervision as possible. Too little exercise is better than too much, and patient, family and assistants must be warned as frequently as possible on the dangers of doing too much. Exercise in warm water is much used in various places provided with suitable pools, and it can also be given in a large bathtub or a Hubbard tub. In the water gravity is largely eliminated and volitional movements can be made that would otherwise be impossible without assistance. This helps the morale of the patient. The principles of muscle protection must always be borne in mind, water or no water. In giving exercises the arc of motion should always be completed even if assistance is needed. Care

should be taken to see that the patient uses the muscles to be excreised and not some other one, as may be done if the patient is not carefully supervised. The amount and the kind of excreise must be modified to suit changes in the condition. With trunk and legs affected weight bearing should not be permitted as long as improvement is going on if the best results are to be obtained. Patients seen late should begin like patients in the neute stage. Muscles that have been damaged by too much use should be allowed to rest in positions allowing the attachments to come as close together as possible and thus make for relaxation Eventually there will come a time when it is evident that there is to be no further improvement, and then with suitable braces the patient may be allowed up and the treatment directed toward getting as good functional use of the body as is possible. Much can often be done in late cases which have been neglected, for often the muscles have been allowed to atrophy from disusc although at present there are more spoiled by too much exercise rather than by too little

It is important to keep the paralyzed limbs warm so as to favor growth, and additional heat should be applied before exercising and once or twice daily in the form of dry heat applied by placing the child or the parts in a tent of hox provided with carbon bulbs. Fresh air and sun baths or ultraviolet ray in the absence of sun is a useful adjuvant in maintaining general nutrition.

Gentle massage is useful in maintaining the nutrition of the muscle, but it should not be used until all tenderness has disappeared and then with caution and the severe hard massage of the professional operator avoided

Warm salt baths may be given daily and are useful in the tender stage to allay the pain and soreness. Children may be bathed in a tub if great care is taken that affected muscles are not stretched. Macanm are advises bathing adults in bed by placing a rubber sheet under them and pinning it with clothes pins to boards hinged to the side of the bed, to the foot and by passing it over pillows to the back of the bed. The water is drained by pulling a part of the sheet through a hole in the board and when not in use the boards are dropped to the side of the bed. Any mechanic can attach gadgets to the bed to allow the use of wires for the same purpose

It is important to keep up the morale of the patient, a thing often neglected. Pity should not be expressed to the patient for it develops the habit of self-pity which is most destructive to the patient's mental well-being. Suitable amusements, and when ready for it education by teachers or by mail games and visitors should be allowed the patient Moderation should be practiced in all things. Only too often patients are left entirely to their own devices and fret and worry in consequence

when a little forethought would render the patient happy and contented. for poliomyelitis victims tend to be cheerful if conditions are at all favorable

The chief points may be summarized as follows

- 1 The tendency is to recovery, much of the permanent paralysis is due to neglect or improper management
  - 2 Contractions and deformity can be avoided.
- 3 The principal thing in the treatment is rest with the body re cumbent but in the position it would be in if standing erect
- 4 The most important muscles should be favored early and until their recovery is assured
- 5 Special adjustments of splinting must be made to favor muscles which should have it.
  - 6 Fatigue general and local should be avoided
- 7 Weight bearing should not be allowed as long as recovery is expected.
- 8 Especial care should be taken not to allow at any time any stretching of affected muscles
- 9 When recuperation is well established, carefully supervised exercise within the capacity of the muscle is of value
- 10 Warm salt baths, very gentle massage (only after all tenderness has disappeared), fresh an and sunlight and warmth are valuable adjuvants in treatment
- 11 The splints or braces should be inspected frequently and changed to suit conditions
- 12 The transition to weight bearing should be gradual, avoiding overexertion and fatigue
- 13 After all the improvement has been obtained that can be looked for as judged by a failure to improve under proper management, the patient should be gotten on his feet, using such apparatus as may be Old and neglected cases will need orthopedic care to correct deformity and exercise to develop latent muscle power
- 14 Every case should be treated individually and not by any fixed Changes should be made to suit conditions as they arise and deformities due to lack of balance of muscles carefully avoided

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# THE INFLUENCE OF FRUIT AND VEGETABLE FEEDING UPON THE IRON METABOLISM OF THE INFANT

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THE iron metabolism of the growing voung has been a question of interest ever since the epochal publications of von Bungel over fifty years ago. His findings that both breast nulk and cow s milk are exceedingly low in iron content and inadequate to cover the iron requirement of the growing organism have not been challenged to this day. It was he who first laid the foundation for the conception of reserve depots of minerals among them notably iron in the growing organism of the young animal to be available when needed during the exclusive milk period.

Haquounenq<sup>2</sup> and, at a somewhat later period, Czerny<sup>2</sup> developed this same conception for the newborn and young of the human species and the latter first called attention to a characteristic alimentary anemia which develops when the young growing organism is deprived of adequate iron intake in its food

The findings of Hart, Steenbock Elveliem and their coworkers and the work of Whipple Robscheit Robbins and others' stimulated a great deal of interest in the subject of alimentary anemia and has in recent years led to a series of splendid investigations in this field

The conception that foodstuffs notably high in iron content, should be curative for alimentary anemia or should be particularly suitable for the replenishment of deficient iron reserves in the organism of the young dates back to the investigations of von Bunge' and is the basis of a feeding régime for the young infant first suggested and cham pioned by Czerny' and now quite generally used in many parts of the civilized world.

The demonstrable high organic iron content of some vegetables and certain fruits suggested them strongly as suitable early dietary additions to prevent the onset of or combat an already existing alimentary anemia. To these were added later for older children, glandular or gans, such as liver or kidney the favorable action of which was recognized by Czerny and others' long before the publications of Minot and his coworkers, although the exact mechanism of such favorable action was not understood at that time

The investigations of Hart and Steenbock' finally showed the re markable effectiveness of combinations of iron salts and traces of copper in the treatment of alimentary anomias and indicated that these substances alone, or preferably in combination with some of the foodstuff mentioned, were a very superior form of treatment for alimentary anemia

The relative degree of effectiveness of these various procedures in combating alimentary anemia was a part of this study, but its principal aim was the study of actual iron retention in the young growing organism to whose dietary were added high iron containing food in the form of vegetable fiber and fruit

In an earlier paper we had studied the effect of vegetable feeding upon the mineral metabolism of the young infant. This included a study of the effect on the iron balance of two of the infants results gave no evidence of a beneficial effect upon the iron retention of feeding dried or puréed spinach. It was felt however, that the evidence was too meager and that the study should be continued with other infants. We are now ready to report results of additional metabolism experiments on three normal infants, ranging in age from five weeks to seven months, and also on one infant diagnosed as a nutritional anemia case As in the earlier work, the vegetable studied has been spinach in the dried, pureed, and raw forms ments have been extended to include the effect of apricots which Whipple and Robscheit-Robbins<sup>5</sup> found more effective than spinach and other vegetables and most other fruits in curing the anemia of their dogs. In the case of the anemic infant, it has also included the effect of adding wheat germ extract, a mixture of ferric and cupric salts and liver

We have attempted to make the experiments as nearly accurate as possible. With very few exceptions, the periods on metabolism have lasted six days. In the case of the anemic infant, the period on milk formula only, used as a control, lasted four days because it was felt that the giving of iron-containing foods should be started as soon as possible.

As a rule the normal infants were very regular in their elimination of feces. No metabolism period was begun until the infant had been receiving a given diet for at least five days so as to insure that its system had reached equilibrium in regard to that diet. Two or three consecutive metabolism periods on a given diet, with one or two days intervening, were run in each case in order to find out what variations may be expected normally when the diet remains constant

The iron content of the various foods was determined by analyses Twenty-five pound cans of powdered milk furnished a uniform stock supply of milk for each infant. The sugar used in the formula was found to contain traces of iron. The amount of milk powder and sugar was increased as the infant grew, but was kept constant throughout a given control period and the following periods in which the supplement of spinach or apprects was added. The dried spinach was

also provided in large lots, each of which was analyzed. The anemic infant was given eight grains daily, the normal infant six grains. The purfed spinach was provided in lacquered tin cans holding a little more than enough for two days' feeding. While a large supply from the same factory batch was on hand and every effort had been made to keep the contents uniform, we felt we obtained a more accurate knowledge of the iron intake by combining together twenty gram sam ples from each can used and analyzing the composite sample for iron The same held true for the raw spinach. The infant's daily allow ance of raw or pureed spinach was seventy grams. Dried apricots were used. They were softened by heating with distilled water on the steam bath and ground to a fine pulp in a porcelain mortar. A com posite, representative of each period, was analyzed for iron. With one exception, the equivalent of forty grams dried apricots were given to the infant daily. Infant No 3 received the equivalent of 57 gm of dried apricots daily in the seventh period. The wheat herm extract was supplied from a large stock solution which had been analyzed for iron content. A water extract equivalent to 16.2 gm, wheat germ was given daily. Iron and copper salts were given to infant No 4 in the last two periods in daily doses of 6 cc of a 10 per cent solution of ferric ammonium citrate (1008 mg Fc) and 15 cc of a 0.2 per cent solution of copper sulphate (0.76 mg Cn.) Liver was freed from connective tissue ground to a pulp and cooked by boiling for a few The daily allowance of liver was 20 gm Iron was deter minutes mined in a composite sample for each metabolism period

As in our earlier experiments the milk formula contained definite weights of powdered milk and sugar made up to a definite volume with distilled water. Any supplement such as the spinach or apri cots was mixed with the milk formula to insure its being entirely consumed. In a few cases especially with the apricots, difficulty was encountered in getting the infant to take all the formula refused to take it or if forced, regurgitated a considerable amount All refusals for a given period were collected. If small in amount they were transferred to a platinum dish, dried ashed and the ash dissolved in a known volume from which an aliquot was taken for analysis If the amount was too large for such treatment it was evan orated to dryness in a porcelain evaporating dish on the steam bath then in an oven at 105° C the residue weighed ground up and mixed and a sample analyzed for iron Regurgitations were caught on masses of weighed gauze and the amount of iron lost in this way calculated from the increase in weight of the gauze and the known composition of the milk mixture assuming one gram gain represented one cc of the mixture lost This, of course introduced an error but a liberal allowance of 10 per cent error in calculation of iron in the regurgita

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these precautions, the obtaining of good checks on duplicate ash solutions meant that any contamination by iron had been avoided

Great difficulty was encountered in finding a suitable method for the iron determination. Almost without exception the methods usually advocated or used by various investigators gave uncertain results and exceedingly poor cheeks of the controls. This experience made us doubtful of some of the reported results, especially of the earlier work on iron

The method finally used for determining iron was a modification of Stugart so method It involved carefully controlled dry ashing in a maffle furnace whose temperature was automatically regulated at 400° C, solution of the ash, partially with N hydrochloric acid and partially, after reashing the residue over the free flame by fusion with sodium carbonate, acid hydrolysis of the ash solution to convert pyrophosphates to orthophosphate, and determination of the amount of iron by colorimetric comparison in amyl alcohol solution against a standard containing 002 mg Fe after adjusting the acidity of both solutions to the same strength and converting the iron to ferric thio cyanate Platinum dishes were used for the dry ashing. The samples were slowly charred by starting them in front of the open door of the mulle furnace and pushing them back gradually avoiding the rapid evolution of gas. With milk samples, a slow charring was made pos sible by mixing the powder with a small amount of water and car melizing by heating overnight in an oven at 105° C before intro ducing into the muffle furnace

### REBULTS

The results of the experiments on normal infants are given in Table I and are shown graphically in Fig. 1 where the heights of the columns represent the values for total iron intake the total iron output and the difference between the two the iron balance. We feel that the results bear out the conclusion we had reached in our earlier experiments, that the feeding of spinach to the young normal infant in any of the three forms tried does not appreciably affect the iron metabolism. We feel also, that the same may be said of the feeding of apricots. The iron balances for a diet of milk only vary within small limits for infant No. 1 all slightly negative for infant No. 2 all slightly positive and for infant No. 3 positive at first but in later experiments slightly negative.

The effects of pureed spinach were tested on two of the infants. There appears to be a slight increase in retention attendant upon the addition of the pureed spinach to the diet if the four periods are averaged a balance of +0.16 mg. Fe as compared with +0.04 mg. the average of the four preceding periods on a milk diet and a larger average of the four preceding periods on a milk diet.

IRON MFTABOLISM OF THE NORMAL INPANT AS INFLUENCED BY THE FEEDING OF SPINACH AND APRICOTS TABLE I

							- 11			
TV AVI	PERIOD	NO DIES				WGT OF	TOTAL	NI 44	FE IN	33
0	ON	7	SUPPI FMENT	HB	ввс	DRIED	PE	FOES	URINE	BALANCE
		PFRIOD	TO MILIC PIET			FECES	INTANE			
				gm per 100 cc	milhons	m m	mg	mg	gm	me a
	H	9	0			4 80	1 16	1 09	0 001	+0 01
	G1	ဗ	0	148	5 06	6 13	1 28	140	0 033	-0 15
	က	9	Spinsch (pur&d)			7 26	2 36	2 33	0 071	<del>†</del> 0 0-
П	7	9	Spinneh (purced)	135	5 52	7 83	5 36	2 26	0 0 34	+0 07
	13	9	_			5 92	146	1 10	0.033	-0 03
	9	9	0	142	5 90	00 9	147	1 56	0 045	-0 14
	۲-	rð	Spinach (raw)			12.96	3 87	3 97	0 021	-0 12
	s	9	Spinach (raw)	154	6 34	17 69	3.78	3 56	0.026	+0 19
	-	0	0			4 80	114	1 03	0 0 0 0 0 0	+0 08
	C1	9	0			4 58	1 29	105	0 041	05 0+
<b>C</b> 3	e	9	c	110	118	464	1 29	1 22	0 024	±0 0±
		າລ	Spinach (raw)			0 40	3 54	3 50	0.036	000
	ະດ	9	Spinneh (raw)	104	4 67	908	3 46	3 07	0 034	+0 30
	1	9	0			69 9	1.37	121	0 037	+0 12
	C1	10	_	155	5.72	6.84	1 30	1 19	0 034	+0 17
	٣	9	Spinach (purfed)			9 93	61	180	0 038	20 10 10 10
	7	9	Spinnch (purfed)	12.2	5 18	8 04	2 23	1 88	0 040	+0 31
	13	9	_			8 52	1 63	140	0 038	+0 10
۴.	9	9	0	153	6 10	9 2 6	1 63	1 57	0 038	to 05
	t-	9	Apricots			11 36	3 08	3 07	0 025	50 O-
	ø	9	Apricote			13 55	3 42	3 44	0 038	90 0-
	G :	ت -	Apricots	94	6 02	11 17	3 34	3 02	0 036	+0 28
	01	9 —	0			7.85	196	2 00	0.024	90 0-
	Ξ;	<b>9</b> •	0	91	50.5	7 19	181	2 05	0.036	-0 28
	21	9	Spinach (dried)	7.8	5 60	11 01	3 42	4 00	0 038	89 0-

balance in three of the four spinach periods than in any of the preceding periods. However, these retentions are small and, we believe, insignificant

The raw spinach, also tested on two infants, gave positive reten tions in two of the four periods studied, while the balances in the preceding milk periods were either negative or if positive, less in amount. Expressed in terms of averages, a balance of +003 mg. Fe on a milk diet was increased to +0093 mg by adding raw spinach to the diet, but again, such a small retention would seem insignificant.

In the case of infant No 1, a severe diarrhea developed as a result of the raw spinach. This was true to a lesser degree for infant No 2. It is interesting to note that in the last period of infant No 1 on raw spinach, there was a fair degree of retention in spite of the greatly increased output of feces. One would feel more optimistic about its favorable effect on iron retention if the first periods on raw spinach for each infant had given positive results. Taking all the effects into account, we feel that the feeding of raw spinach to the young infant is not to be recommended.

Only one metabolism period on dried spinach was tried on a normal infant. The results support our earlier findings that dried spinach, in spite of its high iron content, tends to decrease rather than to increase the iron balance. In this case, a negative balance of 0.68 mg resulted after adding the spinach to a milk formula on which the infant showed an average negative balance for two periods of 0.17 mg. Results of feeding dried spinach to the anemic infant also bear out the same conclusion. Of the three forms of spinach studied, the puréed form would seem to be the only one advisable for infant feed ing, since it tends to increase rather than decrease the retention of iron and can be fed without harmful effects.

The effect of the apricots also appears to be negligible. They were fed only to infant No. 3. During the first of these periods the infant suffered from a respiratory infection which turned out to be very severe. Metabolism experiments with the apricots were continued after he had completely recovered. Whether this affected the iron metabolism during the apricot feeding or not it is impossible to say. The fact remains, however that in only one of the three periods in which the diet was supplemented by apricots was there a positive retention, but this retention was large enough to increase slightly the average retention on a milk diet of +0.060 mg to +0.066 mg. This small effect would seem to be imagnificant.

Hemoglobin determinations (Newcomer method) and red cell counts were made at the end of each of the different diet periods as shown in Table I. Certainly the very small increases in retention

We are indebted to Dr Katauji Kato for all of the hemoglobin determinations and red cell counts.

which occurred as a result of adding spinach or apricots to the milk diet were not accompanied by a rise in the hemoglobin or red cell count of the blood

In both infants, the pureed spinach periods were accompanied by a fall in hemoglobin concentration. The changes with the feeding of

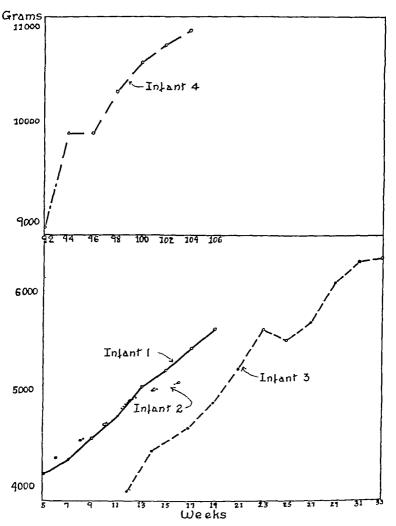


Fig 2—Showing the growth of the four infants whose iron metabolism was studied during the period they were under observation

raw spinach are contradictory. The low values in the later periods of infant No 3 are probably not effects of the apricot or dried spin ach diet but are results of the respiratory infection. With the exception of the low hemoglobin values following an infection, all values for the three normal infants fall close to or above the average value found by Kato and Emery<sup>o</sup> for infants in this vicinity. During the

time they were under our observation, they grew normally as shown in Fig. 2. The average daily retention of iron for the three infants over the period studied was +0.08 mg.

We were able to test the effect of spinach and apricot feeding upon the iron metabolism of an anemic infant in whom there was a definite lack of hemoglobin, possibly a lack of iron because the infant would ent very little except milk. The infant was twenty three months old and weighed 9 kg. He was brought into the hospital with an acute upper respiratory infection which was soon cured. His diet, previous to the time he was admitted had consisted almost entirely of milk. As determined in the clinical laboratory, his hemoglobin was 37 per cent and red cell count 3 100,000

The general plan of feeding follows after a short control period on a milk and sugar diet with cod liver oil, dried spinach was added to the formula in two of the five daily feedings. This diet lasted about three weeks during which time two metabolism periods were carried out. The feeding of spinach was continued, but apricots were then also added to the diet in the remaining three feedings. A period of three weeks on the spinach apricot diet followed and again two metabolism periods were secured. Another similar three-week period followed in which the spinach apricot diet was supplemented by wheat germ extract, a potent source of vitamin B. A fourth three week period studied the effect of a daily dose of 100 mg of iron as ferric ammonium eitrate accompanied by a trace of copper 0.75 mg in addition to the spinach apricot wheat germ diet. Finally the added effect of liver has been studied.

The results are shown in Table II and Fig 3 Weekly determina tions of the hemoglobin concentrations and red cell count of the blood were made Only those at the end of each diet period are given in the tables The chart is drawn to the same scale as the one used for the normal infants but after iron salts were added the height of the columns became so great that they could not be represented in their entirety The results of the iron balance are interesting but perplex ing The two metabolism periods on a given diet agree well with each other thus tending to give confidence in the results as they appear The two periods in which the milk was supplemented by dried spin ach gave one small positive balance followed by a negative balance Certainly the added iron of the spinach was not being utilized output of feces during this period was considerably increased an average daily output of 11 75 gm (measured in terms of dried weight) as compared with a preceding 6 gm daily output When apricots were added the average daily output of feces was reduced to 8 37 gm Correspondingly the output of iron was reduced and the iron bal ance became strongly positive showing an average retention of +2 97 mg Fe Wheat germ extract was added at this point chiefly to com

plete the infant's diet with an adequate source of vitamin B. After the addition of the wheat germ extract, the daily output of feces was 13 96 gm. Again the iron output increased and the iron retention was reduced to an average of +0 09 mg. Fe

The addition of soluble iron and copper salts to the diet resulted in a large increase in iron retention. This was not accompanied by a

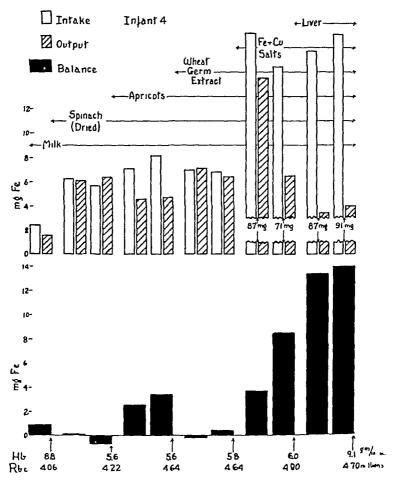


Fig 3 —Showing the iron metabolism of an anemic infant as it was affected by various additions to the diet.

low output of feces, as was the case when a high retention occurred on a milk diet supplemented only by spinach and apricots. The results of these two last periods when soluble iron salts were given agree only fairly well with each other. In the last of the two periods, the intake and output of iron are both smaller, but not in the same proportion so that the retention is considerably greater. There was a smaller output of feces in this period and the increased retention might be explained by assuming that there was an incomplete

IRON METABOLISM OF AN ANEMIC INFANT AS INFERIENCED BY VARIOUS ADDITIONS TO THE DIFF

PERIOD	NO DAYS IN PERIOD	NATURE OF SUPPLEMENT TO MILK DIET	<b>E</b>	n.B.C.	WT OF DRIED FECTS	TOTAL FE INTAKE	72 17 72CE3	FE IN URINE	PEBALANCE
}			gm. per 100 e.c.	millions	Ę	Sm	Яш	Вш	ш
-	4	0	88	4 00	0.00	항	1.64	0.021	98 0+
61	9	Spinach (dried)			11.59	59	0 07	0 0.74	+0 15
•	9	Spinneh (dried)	20	1.93	11.92	5.73	6.7.	0.039	2
4	9	Spinach apricots			8.80	7 11	1,51	0.030	+155
ю	9	Spinach, aprilects	56	<b>10</b> +	7.94	8.00	<b>3</b>	100	+3 39
9	9	Spinach apricots wheat germ			14.73	6.88	7 05	0 037	150-
۲-	20		80	1 60	13.21	0.78	6.35	0 041	+0.30
80	ca ca				13 68	107 19	0F 00	0 045	+3 73
6	9	Fe and Cu salts Same as Period 8	0.0	06 +	70	84 03	75.5-	0.030	+9.47
10	e-	Spinach, apricots, wheat germ,			13 00	101 74	88.30	0 008	+13 37
11	20	Fo and Cu salts, liver Samo as Period 10	0.1	4.70	12.84	107 09	93 05	0 042	+14 00

collection of feces. However, the following facts have to be critically considered. This last period was quite unsatisfactory because the infant exhibited an extreme loss of appetite. Some of the formula was refused and of that consumed, about 13 per cent was regurgitated. The amount of non refused could be determined accurately, but the amount regurgitated was estimated as explained earlier. However, since most of the formula refused contained only milk and spinach, the error introduced was small compared to the retention as calculated. On the other hand, the smaller food intake would account fairly well for the smaller output of feces. We feel, there fore, that the retentions as calculated represent, if not accurate values, at least the order of magnitude of the retention. With the additional feeding of liver, there was a further remarkable increase in the retention of iron although the non content of the diet was scarcely affected by such feeding.

Examination of the hemoglobin concentrations and red cell count of the blood shows that very little improvement took place until liver was added to the diet. There was a gradual increase in the number of erythrocytes, from 406 to 490 million. The hemoglobin concentration fell sharply from an initial value of 88 gm per 100 cc to a minimum of 49 gm at the end of seven weeks. A week later it had returned to 56 gm. From that point on it remained fairly constant until the last week of the period during which soluble iron salts were given when it rose to 60 gm. Whether this meant that the hemoglobin concentration was beginning to increase and would continue so on the same level of iron and copper intake is not known. The feeding of liver was begun at this time and the hemoglobin rose to 98, a rise which was practically maintained during the second liver metabolism experiment.

#### DISCUSSION

The results reported here support the conclusion of earlier experiments that in the case of the normal infant the feeding of vegetables in the form of spinach does not appreciably affect its retention of iron. The same appears to be true of the feeding of fruit in the form of apricots. Whatever increases in the iron retention have resulted by feeding spinach or apricots have been small and apparently insignificant. There has been no increase in the hemoglobin concentration or the number of erythrocytes of the blood as the result of such feeding. On the contrary, there has been a tendency toward a decreased hemoglobin concentration.

The fact that two of the infants showed hemoglobin values considerably above the mean as determined by Kato and Emery<sup>9</sup> for infants in this vicinity would indicate that they had as yet no iron need which was not met by their own reserves or by the iron sup

phed in the milk. There was usually a small retention of iron when the infant was on the ordinary milk formula, and this retention represented only a small proportion of the iron intake. The higher level of hemoglobin concentration for normal infants found by Vackay¹¹ and Bloxsom¹¹ as a result of iron or iron and copper medication does not necessarily conflict with our findings, since we have studied only three infants two of whom had unusually high hemoglobin concentration at the beginning of the metabolism experiments. Whether the high level of hemoglobin would have been maintained had the diet not been supplemented by iron-containing vegetable or fruits is a question for debate. At least, one can say that there was no indication of an appreciably increased iron retention as the result of such feeding which might favor the maintaining of this high level

While the normal infant may not need a greater intake of iron up to the age of six months, another problem is presented in the case of an older infant who has been existing for many months almost exclusively on a milk diet. It is generally conceded that such an infant is not receiving enough iron to maintain the hemoglobin of the blood at its normal level and an aniemia results. When such a case was admitted to the hospital we took the opportunity to determine whether the iron of spinach or apricots could be utilized by such an infant. It was impossible to study the problem rigidly in the one case. Other infants would have to be studied and the problem attacked from different angles. Even such a thing as the form of spinach used would have to be considered, because there seems to be evidence that the iron of dried spinach is not utilized so readily as that of puréed spinach. Our results, therefore can only be considered with much reserve until more data are available.

In the case studied the iron of dried spinach was not utilized but that of the apricots was retained in considerable amounts. Comein dent with this effect perhaps its cause, was a much smaller output of fecal matter after the milk-spinach formula was supplemented by apricots. No such phenomenon was observed when apricots were added to the milk formula of the normal infant. Again after adding wheat germ extract the output of feces increased and the iron retention fell to a low level. We are at a loss to explain such results with out more data. The two periods on an identical diet agree well in each case. Whether this is an accident, and what we have observed is only a normal physiologic variation independent of the wheat germ could not be determined except by repetition of the experiments. For the present we prefer to put the results on record as those of an individual case only.

With the exception of the wheat germ effect, the results of apricot feeding on iron retention were what had been anticipated from the favorable results on hemoglobin regeneration which Whipple and Robscheit-Robbins' had found in the case of feeding apricots to their anemic dogs. On the other hand, we did not get an increased retention of iron with the feeding of dried spinach, such as Krasnoi gorsky's found when the milk diet was supplemented with spinach extract and lactose. Possibly this is explained either by the fact that in the normal infant we found a better retention for pureed spinach than for dried spinach or by the fact that Krasnorgorsky's metabolism experiments lasted only three days, a period which is now considered inadequate for accurate results. Possibly another explanation is offered by the recent report of Schiff, Eliasberg and Joffe<sup>18</sup> that when cow's milk was supplemented by lactose in the diet of rats an increase in hemoglobin concentration occurred

The failure of our spinach or apricot feeding to produce a rise in hemoglobin concentration is contrary to the findings of many investigators, Hart, Steenbock, et al, Whipple and Robscheit-Robbins, Mitchell and Vaughn,<sup>14</sup> Sheets, Fraziei, and Sulzby,<sup>15</sup> Farmer and Corv,<sup>16</sup> and Levine, Culp and Anderson,<sup>17</sup> that the feeding of greenleafed vegetables or of some fruits, such as apricots, to anemic animals (dogs or rats) has resulted in an increase in hemoglobin level interpreting the results with the spinach or apricots, there must also be considered the fact that during the three weeks in which the non of the diet was also supplemented by iron and copper salts in spite of a large iron retention there was no appreciable rise in the hemo globin concentration of our infant, a result which was unexpected in view of the animal experiments of Hart, Steenbock and Elvelijems and the results of the use of iron and copper therapy for anemic infants and children by Josephs, 18 Lewis, 10 and Caldwell and Dennett 20 Possibly we gave too small a dose of iron and copper. It increased the iron intake about twelve times over that in the milk-vegetable diet, but was considerably less than the dose used by Josephs Perhaps we would have had better results with a larger amount of copper believed unwise to increase the dose at the time because of the infant's We hope later to try out the effect of larger doses tendency to vomit of both iron and copper

The fact that the hemoglobin concentration finally rose almost to the normal level after liver was added to the diet is in agreement with the findings of Greengard, Maurer and Kluver<sup>21</sup> in cases of infants whose anemic condition did not respond to iron treatment but who showed improvement after liver extract was also given. In this connection it should be remembered that these investigators found that liver extract alone caused an improvement in the blood picture in 63 per cent of the cases studied, and that in those cases which did not respond, improvement occurred after iron was added

Favorable effects of the feeding of liver or liver extracts in cases of alimentary anemias of infancy have also been reported by Herz, 25

Tuscherer, Ligum, 25 and Strunz 6 We did not try the effect of liver alone. It was believed that the history of the case pointed definitely to a need for iron and that need was supplied by the spinach, apricots, and later, in a much more concentrated form, by the ferric ammonium eitrate. The large retentions of iron, which occurred with the feeding of apricots and soluble iron salts gave evidence that the iron need had been met. That no improvement occurred in the blood picture seemed to indicate the need of a supplementary factor to stimulate the hematopoietic functions to make use of the iron. According to the findings of Hart Stienbock and Flyeligem and Peter son, 27 this should be copper

Whether the increased hematopoietic activity which occurred dur ing liver feeding was due to an increased copper intake or to the action of another supplementary factor in the liver cannot be deter mmed from the data at hand. Another possible explanation might eliminate the liver entirely as a factor and assume that the results were simply a delayed effect of the iron and copper salts because the hematopoietic functions had been reduced in activity to such an ex tent and over such a longth of time that a considerable latent period might be required before stimulation would have its effect. Further experiments along this line are planned. For the present we can only say that the increased iron retentions in an anemic infant which were found as a result of the feeding of approats and to a greater extent with the administering of iron and copper salts, were not immediately reflected in an improved blood picture. There was a later increase in hemoglobin concentration which might have been due either to a de layed effect of the increased iron and copper intake or to some fac tor in the liver which was finally included in the dietary

#### BUMMARY

- I A study of the iron metabolism of three normal infants, ranging in age from five weeks to seven months, has shown that vegetable (spinach) or fruit (apricots) feeding in addition to the milk formula exerts no significant effect upon the amount of iron retained by the infant. Such feeding increased the iron intake 60 to 171 per cent. The hemoglobin concentration and the number of crythrocytes in the blood were within or above the normal range for infants of this vicinity and age and were not raised by the vegetable or fruit feeding.
- 2 A study of the effect of such feeding upon an anemic infant, twenty three months old who had been hiving on an almost exclusive milk diet, has shown a lack of effect in the case of dried spinach, but a marked increase in retention of iron when apricots were added to the diet, an effect which disappeared again after wheat germ extract was also included. The effect in each case is related to the amount of

fecal matter eliminated in the metabolism period. We prefer to with-The hemoglobin hold interpretation until more data are available concentration and erythrocyte count of the blood were not improved during the course of such feeding

3 A very large increase in the concentration of soluble iron in the diet of the anemic infant, brought about by adding feiric ammonium citiate, resulted in a large increased retention of iron, but up to the end of three weeks on the diet, only a very slight increase in the number of erythrocytes had occurred and practically no change in hemoglobin concentration

4 When the diet of the anemic infant was further supplemented by liver, the retention of iron was increased still more tion in this instance was accompanied by a rise in hemoglobin from 60 to 91

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# CHOLESTEROL PARTITIONS OF THE BLOOD IN MYXEDEMA (CRETINISM)

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I T IS known that disturbances of the thyroid gland are associated with a disturbed cholesterol metabolism. The total amount of cholesterol in the blood is normally from 100 to 230 milligrams in 100 c c <sup>1</sup>. In both clinical and experimental hyperthyroidism<sup>2</sup> the blood cholesterol tends to be reduced. In hypothyroid states the total blood cholesterol tends to be increased <sup>2</sup>.

Because of this association, Epstein and Lande<sup>4</sup> studied the level of the blood cholesterol and the level of the basal metabolic rate. They found an inverse ratio of the basal metabolism and the blood cholesterol which they explained on the basis of an increased rate of oxidation. This caused increased consumption of available lipoid with reduction in the blood and vice versa.

In general, we may say that there seems to be a fairly definite relationship between the basal metabolic rate and the cholesterol level of the blood in myxedema. In untreated myxedema, the cholesterol is increased and the basal metabolism is decreased. As the basal metabolic rate is raised by thyroid therapy, the blood cholesterol is lowered. We were able to observe a case of a twelve-year-old untreated cretin in our wards who illustrated the almost mathematical relationship between basal metabolism and blood cholesterol. Fig. 1 shows graphically what occurred with thyroid therapy

In nephrosis the blood cholesterol is usually increased. The subnormal basal metabolism, when it occurs, is probably not due to hypo thyroidism, but perhaps to defective protein metabolism. However, even in nephrosis, Epstein and Lande' found a similar inverse relationship between basal metabolic rate and blood cholesterol level, as both were influenced by thyroid therapy. We were able to study a group of cases of nephrosis in children between the ages of two and ten years. We may say that in our cases fluctuations in the level of the blood cholesterol were quite independent of thyroid therapy. There seemed to be no constant relation between the level of the blood cholesterol and the basal metabolism. From our experience therefore, we can corroborate the findings of Epstein and Lande in so far as myxedema of endocrine origin is concerned, but not for nephrosis

From the Wards of the Pediatric Department and the Laboratories of The Yount Sinal Hospital, New York.

Cholesterol appears in the blood uncombined or as free cholesterol, and as cholesterol ester. The relative proportion is free 20 to 50 per cent, ester 50 to 80 per cent. This relationship normally is quite constant regardless of the total amount of cholesterol present. In pregnance Bloor and Knudson's find a relative increase in the ester and Knudson's says there is also an increase in ester after feeding a high fat diet. In cases of mechanical interies, the cholesterol ester is often diminished. Thannhauser's showed that in conditions of liver atrophy there is a decrease of ester, which may go on to a complete disappear ance. This has been verified by F. Z. Epstein.

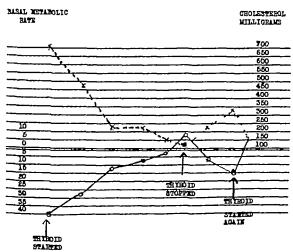


Chart I—Relationship of cholesterol level to basal metabolic rate under thyroid therapy in cretin (Case 5)

Table I shows the cholesterol determinations in a case of subacute yellow atrophy of the liver studied on our wards, which corroborates Thannhauser's and Epstein's findings.

TABLE I

			FREE	REMARKS
DATE	TOTAL CHOLESTEROL	ESTER.	The	
Oct. 81, 1931 Nov 14 Jan. 4 1032 Feb. 15 Mar 4	187 198 115 100 80	82 29 faint trace 19 faint trace	105 169 115 81 80	H G a girl 8 years old

Postmortem findings showed complete destruction of normal lobular markings of the liver

Liver damage, we believe is the only known condition in which the ester concentration in the blood stream is markedly decreased

In studying the cholesterol of the cretin cited above, we found such a marked diminution in the ester of the blood, especially in relation to the free cholesterol, that the ratio usually found in the normal between ester and free cholesterol was reversed. In order to determine whether this was an accidental finding or whether there is actually a decrease in the ester in the blood in myvedema of childhood, we studied the blood cholesterol partitions of eleven cases of myvedema (cretinism). The findings are given in Table II

TABLE II

CAS	Ε	ACE		TOTAL CHOLES TEP 01	ESTEP	FI EE	виг	estep %	PEMAPKS THYROID THEKAPY
1	5	vear-	đ	470	210	260	minus 2%	44%	treated since 21/2 years
2	4	vears	ô	210	90	120	not done	43%	treated since 21/2 years of age
3	9	vears	ð	190	75	115	plus 3%	38%	treated since infancy
4		vears		250	95	155	plus 1%	38%	treated since 5 months old
5	12	vears	Q	676	270	406	minus 39%	20%	untreated Feb 13/31
				120	70	50	plus 8%	58%	treated March 17/31
b	1°	venrs	φ	170	100	70	plus 9%	58%	treated since 2 months old
7	8	verrs	₽	290	135	155	minus 19%	48%	treated on and off since 8 months of age
S	4	venrs	₽	320	90	230	minus 19%	28%	mvvedema developed at age of 2, un treated
9	6	vears	₽	215	86	129	not done	40%	treated since early
10	13	vears	φ	340 300	$\frac{195}{200}$	145 100	not done	57% 66%	treated since childhood
11	6	venrs	₽	200	100	70	not done	50%	treated since early childhood

Male o Female 9

It will be seen from columns 3 and 4, that instead of the normal ratio of 50 to 80 per cent there is frequently a decrease, so that there is less ester than free cholesterol. This was noted in all cases except Cases 5 6, 10 and 11

After intensive treatment with this roid, Cases 5 and 6 had a fairly high basal metabolism, quite normal however, for their age, as the basal metabolism in childhood tends to be high and the ratio ester to free was normal. It is possily that it determination of the cholesterol fraction is of value in the conjunction of the therapy, and abolic rate may be an aid in judging the result of the cholesterol fraction and explanation of the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction is of value in the cholesterol fraction in the cholesterol fraction is of value in the cholesterol fraction in the cholesterol fraction in the cholesterol fraction is of value in the cholesterol fraction in the cholesterol fraction in the cholesterol fraction is of value in the cholesterol fraction in the cholesterol fraction in the cholesterol fraction in the cholesterol fraction in the cholesterol fraction in the cholester

<sup>\*</sup>The basal metabolic rate was charted against total calories referred to age—a standard which Talbot considers the best for cretins in judging effect of thyroid therapy

tamly not lay the decrease to some dysfunction of the liver—Rather we quote Thannhauser, 10 "In atrophy of the liver the total cholesterol in the blood is reduced and the ester is almost absent—Diametrically opposed to this we have shown, that in animals in whom the liver has been removed, the total cholesterol in the blood is increased, especially the ester portion—The liver may be responsible for the ratio cholesterol ester to free cholesterol in the blood." At present therefore this statement expresses very concretely the extent of our knowledge of cholesterol in the blood which we hope may be enlarged by the investigation of more material, especially in untreated or poorly treated cretims.

#### BUNMARY AND CONCLUSIONS

In myxedema of hypothyroid origin, there is a very definite inverse relationship between the total cholesterol level and the level of the basal metabolic rate, the cholesterol is high the basal metabolism low. When thyroid extracts are administered, the basal metabolic rate rises, and the level of the total cholesterol simultaneously falls to normal (below 250 mg.) In nephrosis, although the total cholesterol is in creased, and the basal metabolism may be decreased, there is no constant relationship between the two, nor is there any predictable effect of thyroid therapy

Cholesterol appears in the blood in the free state and as cholesterol ester the relative proportion being—free, 20 to 50 per cent, ester, 50 to 80 per cent

The only known pathologic condition in which the relative propor tion is reversed is liver atrophy, in which condition there is a decrease of ester, which may go on to almost complete disappearance

This paper reports the results of a study of the proportion of free cholesterol to ester in 11 cases of myxedema of hypothyroid origin. In all but four of the cases the ester was reduced, so that the normal ratio of combined (ester) to free cholesterol was reversed a reversal which as far as we could ascertain from the literature occurs only in hepatic dysfunction. In these four cases the lowest figures in the group for total cholesterol was obtained, and the ratio of ester to free cholesterol was normal they also had the highest basal metabolism in the screes—perhaps the most normal for the age as the basal metabolism in childhood tends to be rather high than low

It seems that in myxedema of childhood (cretinism), not only is the total cholesterol increased but at times the ratio of ester to free choles terol is disturbed, so that the relative proportion is reversed. This ratio may become normal after intensive treatment with thyroid extracts

It is possible that in the determination of the ester to free choics terol ratio we may have a valuable diagnostic aid to thyroid therapy in this condition

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#### INTERPRETATION OF BASAL METABOLISM OF CHILDREN

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The portable metabolism apparatus which was hardly seen outside of hospitals a dozen years ago, is now frequently included in the office equipment of physicians in many parts of the country. This means that metabolism determinations, which at first could be made only by a few specially trained investigators, can now be included in most clinical studies of obscure disease. The purposes of this paper are to summarize the knowledge required for clinical inetabolic tests and to indicate in so far as possible the errors to be guarded against in obtaining and interpreting metabolic data. Although many of the factors to be mentioned are significant in studying the basal metabolism of adults, they are here considered chiefly from the pediatrician's viewpoint.

The methods of obtaining metabolism measurements fall into two categories—the indirect and the direct. When the indirect method is used, the amount of heat produced by the patient in a given length of time is not determined per se, but is calculated from measure ments of the exygen consumption. The direct method involves meas urement of the heat production itself. For this direct calorimetry, the patient must be placed in a closed chamber equipped with suit able recording mechanisms This is the more comfortable method for the patient, but it requires apparatus not available to the practitioner in most places. The discomforts involved in indirect measurement of the heat production (portable apparatus) are not severe and cause relatively little disturbance of physiologic conditions once the pa tient has become accustomed to them. The patient lies quietly on a couch for a brief period breathing through a rubber mouthpiece con nected with the oxygen supply and recording apparatus breathing is prevented by a clip. The test is easily performed and the technic can be learned in a short time by any one accustomed to simple laboratory procedures If directions are followed accurately. there is little chance of introducing errors other than those inherent in the method itself

The majority of inaccuracies are due to failure to establish "basal conditions" before and during periods of observation. Lack of co operation, and the exeitement or nervousness of the patient due to fear or unfamiliarity with test conditions during the first observations and nervousness and lack of tact on the operator's part are the most frequent causes of unsatisfactory measurement. Work with children requires special knowledge and experience as well as the even temperament and easy manner which inspire confidence. Without

these, measurement is impossible, for true "basal conditions" cannot be established or maintained during the period of observations unless the child is essentially contented. Basal figures can rarely be obtained from children during the first test period because of lack of adjustment to the necessary conditions. Frequently, it is impossible to get significant data on the first day that the child is tested. Readings should not be considered basal unless those taken during two periods agree within 4 per cent. Satisfactory figures can rarely be obtained by means of the portable apparatus from children less than eight years old.

Individual measurements are of little significance, of course, unless compared with a definite standard. The methods by which the various available tables have been compiled should be thoroughly understood before results are interpreted, if conclusions are to be valid. No figures should be blindly accepted at face value, for the effect of certain important factors cannot be included in the standard tables. In the tables constructed from the findings of Benedict and Talbot, the figures given for children less than two years of age are not strictly comparable with those for older children because they were obtained shortly after the babies had been fed. They do, however, fulfill all other requirements of basality and therefore constitute a suitable basis for comparison. The data for children less than eight years old were obtained in the cot-chamber, those for older children by the portable apparatus in most instances.

The standards for metabolism, like those for height and weight, are average figures. Since they are not absolute, it must always be remembered that the limits of normal lie above and below the figure given. In adults, normal variations may amount to as much as 10 per cent in either direction, in children, interpretation is more difficult because a larger proportion of measurements falls outside these limits, the proportion decreasing with age. More care is therefore necessary in the interpretation of slight deviations in young patients

The fact is now generally accepted that the amount of heat produced depends upon the amount of active protoplasmic tissue in the body, that is, for the most part upon the size of the muscles and internal organs. Inactive tissues like bone, fat, and the body fluids do not produce heat. Since the relative proportion of active and inactive tissue in the body varies greatly with different individuals, and may vary considerably in any one individual at different times, figures obtained from metabolic studies may at first glance appear misleading. Interpretations consistent with clinical experience can be made only after the ratio between the two types of tissue has been estimated. Metabolic data obtained from children of average normal development that is whose weight corresponds closely to the average for height and sex, can be compared satisfactorily with all available

standards (calories per square meter of body surface, calories per kilogram of body weight, total calories for age, total calories for height, total calories for weight) Metabolic data from thin or fat children, on the other hand, must be interpreted with care, for the make up of the body has a great effect upon the significance of the figures Unless weight is approximately average for height and sex. metabolic data cannot be compared with any standard in which total heat production is divided by the weight-alone or as part of some formula, for example, with tables of the average number of calories ner kilogram of hody weight or of the number of calories produced per square meter of body surface. In the latter case, the surface area of the body is estimated from a formula which includes weight is possible partly to compensate for errors which arise in this manner by making certain corrections, but in actual practice it is more satis factory to compare the data obtained from fat or thin children with both weight and height tables (see Tables I and II) and to estimate the significance of the figures from the discrepancy between the two There is no standard of metabolism from which to draw conclusions about individual measurements with mathematical accu racy, because of the great variety of factors involved. No table can be constructed to take all of these into account, but all factors should be considered in the diagnosis of each individual

Measurements obtained from tall and short children of average weight for height are comparable with standards of calories per square meter, calories per kilo, and total calories for height and weight Figures from underweight children are comparable with total cale ries for height, total calories for expected weight calories per kilo of expected weight and calories per square meter of body surface if the expected weight and not the actual weight is used in the formula for figuring area of body surface. If the actual weight is used in the last two calculations, the metabolism will appear increased, although it actually is normal in terms of total calories for height. The metabo ham of children who are obese (i.e., weigh 20 per cent or more above the average for children of the same height) shows the opposite effect until the extra activity involved in carrying the fat causes superior development of the muscles The calories per square meter and per kilo tend to fall below normal, and the total calories for height and for weight are normal After superior muscular development takes place, the metabolic figures are higher than the standard total calo ries for height and correspond closely to the total calories for weight The same effects may be seen whenever weight is added to the body in the form of mactive substance, for instance in edema and ascites

Table III gives an indication of the importance that may be attributed to percentage deviations from the standard metabolism when

TABLE I

BASAI 24 HOUR HEAT PRODUCTION OF BOYS AND GIRLS FROM THE FIRST WEFK
APTER BIRTH TO 12 YEARS OF AGE, PREDICTED FROM HEIGHT\*

AFT	ER BIRTH TO	12 YEARS OF	Age, Predicter	FROM HEIG	HT*
неіснт	PREDIC	TED HEAT		PREDIC	TED HEAT
	BOYS	GIRLS	HEIGHT	BOYS	GIRLS
cm	cals	cals	cm	cals	cals
48	~	122	100	775	675
49	~~~	136	101	785	685
50		150	102	790	693
51	160	165	103	795	700
52	170	178	104	800	711
53	185	194	105	805	720
54	198	208	106	810	730
55	210	222	107	815	740
56	225	236	108	820	749
57	238	250	109	825	759
58	260	268	110	830	769
59	280	283	111	840	778
60	300	300	112	850	788
61	310	318	113	855	797
62	315	332	114	865	807
63	330	350	115	875	817
64	358	367	116	885	828
65	384	384	117	895	837
66	390	401	118	910	847
67	400	418	119	920	857
68	420	435	120	935	866
69	435	452	121	945	875
70	450	468 483	122	955	885
7 I 72	465	1 483	123	965	894
72 73	480	500	124	980	904
74	495	516	125	990	915
75	510 525	530 543	126 127 128 129 130	1000	925
76	535	557	127	1015	935
77	555	567	128	1025	945
78	565	575	129	1035 1045	956 965
79	577	583	131	1045	975
80	500	586	132	1072	985
81	600	591	138	1083	995
82	612	595	134	1095	1005
83	620	598	135	1105	1016
84	622 635	602	136	1115	1026
85	645	605	137	1130	1037
86	660	607	138	1140	1047
87	670	610	139	1152	
88	685	612	134 135 136 137 138 139	1165	
89	695	615	141	1175	
90	705	617	142	1187	
υI	715	620	143	1200	
<b>63</b>	725	623	144	1210	
93	730	626	145	1220	
94	740	630	146	1232	
95	745	637	147	1232 1242 1255	
96	755 760	644	148	1255 1268	
n7	760	651	149		
98	765	659 667	150	1280	
99	770	00/			

\*Talbot F B Physiological Reviews 5 No 4 pp 490 491 October 1925

compared in the manner suggested above. In Table IV are listed a few conditions in which the metabolic level is of special interest

It is technically easy to determine the metabolic level, often difficult to establish and maintain basal conditions, particularly in chil-

TABLE II

BASAL HEAT PRODUCTION OF BOYR AND GIRLS PER 24 HOURS PREDICTED FROM
RODY WEIGHT

BODY WEIGHT (WITHOUT CLOTHING)		ICTED SAT	DODY WEIGHT (WITHOUT CLOTHING)		ICTED	BODY WEIGHT (WITHOUT CLOTHING)		ICTED SAT	BODI WEIGHT (WITHOUT CLOTHING)		ICTED EAT
WIT CLOT	BOYS	onts	TODY CLOT	вотв	GIRLS	1000 CT 01	BOYS	GIRLS	SODY (WI CLOT	BOYS	GIRLS
kilos	cals.	cals	Lilos	cals	cals	Lilos	cals.	cals	Lilos	cals.	cals
2.5	115	110	11.5	607	595	20.5	878	818	295	1103	1032
8.0	150	150	12.0	625	010	210	885	830	300	1115	1045
3.5	180	185	12,5	648	675	21.5	898	842	305	1127	1058
40	210	220	180	660	640	22.0	910	8ა5	31.0	1140	1070
4.5	240	2.3	186	6.8	652	22.F	925	867	315	1150	1080
50	270	285	14.0	695	66u	230	940	880	32.0	1100	1000
5.5	300	318	14.5	710	678	23.5	953	800	32.5	1170	
60	330	350	150	725	090	24 0	965	000	33 0	1180	İ
6.5	860	377	155	740	700	24.5	978	915	83.5	1190	l
70	390	405	160	7.5	710	250	990	930	34 0	1200	i
7.5	418	482	165	768	722	2 , 5	1005	940	34.5	1210	ļ .
80	445	460	170	780	73-∋	26 0	1020	950	350	1220	
8.5	470	480	17 5	793	747	26.5	1033	962	35 5	1230	ļ
9 0	495	500	180	805	760	27 0	1045	975	300	1240	
9.5	5°0	520	18.5	818	7:0	27.5	1058	987	36.5	1248	1
100	545	540	190	880	780	28 0	1070	1000	370	1235	
10.5	568	500	19.5	845	793	28.5	1080	1010	87.5	1265	j
11 0	590	580	900	860	805	29 0	1090	1020	380	1275	1

From Benedict and Taibot Carnegie Inst. Wash., Publication 30., p 06

Low

TABLE IV
CONDITIONS IN WHICH THE METABOLIO LEVEL IS OF INTEREST

METABOLIC LEVAL				
DEPRESSED	NORMAL	ELEVATED		
Subnormal temperature	Edema	Fever		
Severe chronic malnutrition	Mongolianism	Hyperthyroidism		
Hypothyroidism (myxedema)	(usually)	1		
Hypoadrenalism (Addison a discuse)	Eesema (usually)	l .		
Hypogonadism (probably)	Ichthyosis (usually)	1		
Mongolianism (occasionally)		1		
Eezema (occasionally)	ļ	1		
Ichthyosis (occasionally)		1		

dren, and always very difficult to interpret intelligently the figures obtained without knowledge of all the technical and physiologic factors which affect the significance of the standards

TABLE I

BASAL 24 HOUR HEAT PRODUCTION OF BOYS AND GIRLS FROM THE FIRST WEEK
AFTER BIRTH TO 12 YEARS OF AGE, PREDICTED FROM HEIGHT\*

AFTER BIRTH TO 12 YEARS OF AGE, PREDICTED FROM HEIGHT*						
HEIGHT		TED HEAT	HEIGHT	PREDIC	TED HEAT	
	BOYS	GIRLS	HEIGHT	BOYS	GIRLS	
om	cals	cals	om	cals	cals	
48		122	100	775	675	
49		136	101	785	685	
50		150	102	790	693	
51	160	165	101 102 103	795	700	
52	170	178	104	800	711	
53	185	194	105	805	720	
54	198	208	106	810	730	
55	210	222	107	815	740	
56	225	236	107 108 109	820	749	
57	238	250	100		749	
58	260	268	110	825	759 769	
59	280	283	110	830		
60	300		111	840	778	
61	310	300	112	850	788	
62	310	318	113	855	797	
63	315	332	114	865	807	
64	330	350	115	875	817	
65	358	367	116	885	828	
66	384	384	117	895	837	
67	390	401	118	910	847	
01	400	418	119	920	857	
68	420	435	120	935	866	
69	435	452	121	945	875	
70	450	468	122	955	885	
71	465	483	123	965	894	
72	480	500	124	965 980 990 1000	904	
73	495	516	125	990	915	
74	510	530	126	1000	925	
75	525	543	127	1010	935	
76	535	557	128	1025	945	
77	555	567	129	1035	956	
78	565	575	130	1045	965	
79	577	583	131	1060	975	
80	590	586	132	1072	985	
81	600	591	133	1083	995	
82	612	595	134	1095	1005	
83	622	598	135	1105	1016	
84	635	602	136	1115	1026	
85	645	605 607	137	1130	1037	
86	660	607	138	1140	1047	
86 87	670	610	139	1152		
88	685	612	140	1165		
89	695	615	141	1175		
90	705	617	142	] 1187 ]		
91	715	620	143	1200		
92	725	617 620 623	144	1210		
93	730	626	145	1220		
94	740	630	146	1232		
95	745	637	147	1242		
96	755	644	148	1255		
97	760	651	149	1268		
98	765	659	150	1280		
99 (	770	667				
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\*Talbot F B Physiological Reviews 5 No 4 pp 490 491 October 1925

compared in the manner suggested above. In Table IV are listed a few conditions in which the metabolic level is of special interest

It is technically easy to determine the metabolic level, often difficult to establish and maintain basal conditions, particularly in chilregulation which intrauterine life characteristically provides. How often for example, does a premature infant of 1000 gm double its weight in the succeeding forty four days to keep the pace of more fortunate fetal contemporaries? Here indeed, we may truly say, is real growth but since it is rarely attained in a similar case under ordinary conditions of actual practice we are bound to inquire into the problem and the more so, when we compare the beautiful uniformity of data displaying the course of normal fetal growth with the vastly different and highly irregular trends commonly witnessed during corresponding intervals of postnatal existence

Chineal interest in the matter of growth takes its origin most conveniently at birth. Among questions relating to growth and having considerable clinical importance even at this early stage of life are those regarding the viability and as already noted the development of the premature baby the cause of birth, and the physiologic loss in weight but their discussion must wait consideration of somewhat more fundamental problems

Succeeding birth, we are wont to observe a young subject develop as the process of growth unfolds itself, and always to do so no doubt with a considerate and humble amazement at the regularity, and one may even add at the biologic precision with which the familiar landmarks are reached and passed. What, we ask, can this be, or failing the ultimate answer, what are the significant features of the process, how are they to be recognized or interpreted and what must be done to preserve them! We ask also that the answers he simple else our new knowledge can hardly have practical worth maist on the latter stipulation, we imply a priori that the laws of growth are themselves simple and of this there is much legitimate doubt We shall not, moreover, he spared a certain disappointment if we cannot at once accept the fundamental tenet that we deal in any form of growth, with one of nature a most complex mysterics In fact it is easy to reach such a conclusion by examining a few ele mentary propositions

#### REMARKS AS TO THE SIMPLICITY OF THE LAWS OF GROWTH

From the biologic point of view all growth is truly a matter of cellular multiplication. Let us set down then the simplest possible law of growth which with certain reservations, is this Cellular reduplication, once initiated, will continue uniformly in its state of motion until acted upon to change that state. But in so doing we have already made three important assumptions regarding the nature of growth first that growth consists of an increase in cell number, second that there exists something which will enable cells to reduplicate and third that there is something else which may or may not inhibit the process. A more complete statement, consequently would

require additional investigation into and specification of, each of these three postulates, to say nothing of an examination of the rather evident implication that growth once initiated will proceed, other things being equal, in purely geometric fashion

Now, it happens that the geometric type of reduplication is re peatedly approximated in every bacterial culture, that it is witnessed unequivocally in successive generations of paramecia, or in tissuecultures, and that it even appears to quite a recognizable extent during the embryonic phase of human growth. But it is in this sense, and only in this sense that the law or its application remains "simple", for experience shows, as even Lucretius1 knew, that reduplication under ordinary conditions of life comes sooner or later to a close Our lines of inquiry must therefore be directed at the agencies which can and do affect the state of growth, as well as into those "things" which cannot now obviously remain "equal" Yet even if these circumstances may ultimately prove to be themselves of quite a simple nature (though this is also highly unlikely), we have departed from the simple to deal actually with something definitely complex 18 this all, for we have thus far just mentioned the matter of growth initiation, but not how this may be presumed in simple fashion to come about Still, our main object of the moment has been achieved, for it is now evident that, if we seek and later obtain rudimentary relationships, we shall be able to deal only with rudimentary events, that the laws of growth, instead of being themselves simple, must clearly be organized combinations of more elementary statements, and finally that rugged simplicity in the case of human growth is beyond the range of expectation

The preceding remarks are not intended to mean that the problem is any less soluble than before Indeed, the reverse is actually true, for, as a result of all the work done previously, we are in better position than ever to recognize and to proceed with further projects Modern knowledge of infant feeding with its heritage of the past has made us all familiar with the energy requirements of growing chil Studies of nutrition during the last quarter of a century, so ably presented and interpreted by Czerny in his classical work on the subject, have placed at our disposal a myriad of facts of everyday use, albeit that much of this information on growth has been collected, interestingly enough, through observations of the very process whose fundamental nature still remains obscure Thus the indispensability of tryptophane, or of other amino acids, the similar and equally important need for the vitamins have in great part been established by observations which compared growth in the experimental animals with that in appropriate controls Such studies are, however, more properly concerned in the last analysis with the fuel of growth rather than with growth itself Still, on the basis of this vast and

solid foundation there can be no hesitancy today in accepting the view that all growth depends directly upon a suitable source of nutriment, and hence, in Spencer's terms, upon energy exchange as well

In addition to this knowledge of fuel intake we possess reliable, though perhaps not complete, information on energy, or better, heat elimination. We know further, much about the natural course of growth, as this is recorded by incremental change from time to time We need next a glimpse of what goes on in conjunction with and at the time of reduplication From the dynamical point of view noth ing would serve so well as some convenient measure of energy ex change, provided we knew the relation between growth on the one hand and say heat production on the other Until recently no such direct relationship has been brought forward, our own results, else where presented, affording, we believe, some insight into the connec tions between growth and basal metabolism. It should, therefore, ultimately be possible to consider some of the underlying events as well as their clinical significance from each of these essentially practical points of view. Here, however it will be best to devote some preliminary attention to definitions especially to that of growth it self, to a consideration of the matter of size, as regards mass or length, and finally to a brief description of the scheme of energy ex change upon which the dynamical connection of growth and metabolism has been found to depend

#### DEFINITIONS

In treating the problem of growth primarily from the clinical point of view it is comparatively easy to set down and to accept almost any of the definitions of growth thus far proposed. This is so chiefly because the normal organisms with which we deal are fully differentiated at the time of, and for that matter, even considerably before birth. It is unnecessary therefore to place emphasis upon processes such as that of tissue differentiation, which at an earlier stage nor mally accompany and are so closely associated with growth itself that it is not always possible to distinguish or to deal with either of them separately. Consequently, it is quite reasonable to consider the human infant as representing an organized group of various cell populations, and on this basis we shall treat the case of human growth much in the manner of dealing with the simpler example of growth among unicellular colonies

The Definition of Growth—The matter of definition is of particular import chiefly because it has been found necessary to alter slightly but significantly the almost universal opinion that growth is to be defined in the broadest sense as increase in size. The latter, to all intents and purposes seems logical enough, and it has thus been adopted by many writers on the subject. An excellent expression of

this view has been given by Julian Huxley wherein he speaks of growth as "a process of self-multiplication of living substance," a statement that is evidently quite in accord with the suggestion just previously made to the effect that we shall here treat the human infant as an organization of various cell-populations upon whose reduplication growth is considered in chief part to depend

There has, of course, been perennial conflict as to whether in the human case, for example, size should be measured preferably in terms of length, mass, or even volume, it being clearly impossible to estimate size in terms of cell number. To this particular matter we shall return later, it is more important just now to see that such discussions must always remain somewhat beside the point as long as the definition of growth itself must be held in question, for even though final agreement as to the best measure of size may ultimately be obtained, we would still be left with the impression that growth is, and can only consist of, an increase in size

We prefer instead, on the basis of results outlined elsewhere,3 to conceive of growth as associated with a change in size rather than to specify that growth consists exclusively of an increase in size the practical point of view, of course, it is immaterial whether we speak of the usual form of growth as a change or as an increase in size because the increments accompanying normal growth are obviously positive But the distinction just noted is important to a clearer understanding of the fundamental factors which together effect, and for that matter control what is commonly called growth case will illustrate the usefulness of viewing the problem in terms as general as these We know, for example, that appropriate quantities of suitable food will sustain the growth of a young infant or of some young experimental animal, we know also that abstinence from food cannot be followed by continuous increase in weight, and indeed that the reverse is always true We are thus confronted with the alternative of calling the positive changes growth, the losses starvation, and the entire scheme something else, as though each of these events were essentially different transactions without bearing upon, or without any relation, save that already mentioned, to each other, or, of taking the simpler position that all changes whether positive or negative, and hence quite independent of food supply at all, are dominated by a single process which succeeds under normal circumstances in producing the result called growth, or under "abnormal" conditions, in traversing with equal certainty the path recognized broadly as star-The fundamental phenomenon is thus made to take the name of its more conspicuous subsidiary, whence it is natural to regard the entire aftair as a problem in the "motion of growth" Support for this suggestion is found not only in the fact that the actual course of starvation may be predicted from the equations of growth for the case

of complete or even partial removal of food, but also in the fact that the trend of basal metabolism during starvation is just as definitely accounted for as it is during the normal course of growth.

Thus far, however, we have not defined growth in sufficiently exact terms, for study of the subject clearly reveals that there is something more to the quantitative character of growth than mere change in size, there is, in fact, no difficulty in realizing that the latter description concise as it is, refers, and can refer only to a difference in size at two succeeding times, and thus to a gain if the difference be positive, or to an actual loss if the reverse be true. Growth, on the other hand, in its purest form, is intrinsically a matter of cellular reduplication and not one of simple change in cell number it is, moreover, clearly dependent upon energy exchange, and it is likewise subject, as we have elsewhere shown, to actual dynamical constraints, whence we are easily led to consider all growth a mode of motion the essence of which is held to be change in size per unit size

The capital differences between "true growth" and "ordinary gain" as just described, are set out in Table I where items (2) and (3) represent in mathematical notation the quantities likewise given by items (1) and (4) respectively

TABLE I

COMPARISON BETWEEN TRUE GROWTH AND ORDINARY GAIN

	OROWTH	GAIN
(1) Definition	Change in Size per Unit Size	Change in Size
(°) Quantity	$q = \int_{0}^{t} \frac{dx}{dt} dt = \text{Log}_{\frac{\pi}{2}}$	$\int_{0}^{t} \frac{d}{dt} dt = s - \gamma$
(3) Instantaneous Rate	$\frac{dq}{dt} = \frac{1}{\sigma} \frac{d\omega}{dt}$	$\frac{dz}{dt}$
(4) Unit of Rate	Kg/Kg./T	Кg/Т

The letter z represents size in terms of mass, length or cell number

The preceding statements and the data in the table thus emphasize what may be termed the relativity of growth," a point of view by no means distinctly new for Minot's as early as 1891 recognized its importance and made the first clearly conceived efforts to compute by approximation what he properly termed 'the rate of growth' and what may also be called in the usual case, the relative rate of gain The success of more recent investigators, incidentally, in dealing mathematically with certain forms of growth is especially noteworthy in the case of those who employ expressions based upon or directly related to an equation first proposed by Benjamin Gompertz's in 1825, which implicitly takes account of this 'relativity of growth''

Size -With this particular conception of growth itself in mind, we are next confronted by the traditional problem regarding size Here, however, greater leeway is permissible, and it may be admitted that the specification of size can, for the most part, be quite properly decided, in the individual case, on the basis of suitability or even of convenience From the biologic point of view the most generally acceptable measure of size is clearly cell number. This is a unit which may be immediately applied to the case of growth in unicellular populations, though it suffers in the case of the higher forms in part from the fact that not all cells of such an organism are either alike or themselves of identical size. But the greater difficulty in these instances is to count the cells, and we are therefore required to express size in terms either of length or mass. A choice between the two is again purely a matter of convenience, provided we desire to use but one of these dimensions, for mass is itself a function of length via the property of density, and so long as the latter remains constant it is unimportant from this standpoint alone, whether we determine size as a function of length or of mass. In a complete analysis, and in the most general case where length and mass are understood to vary independently, each will need to be considered, but, since it is always prefeiable to work as long as possible with a single dependent variable, we approach the study of human growth best of all in terms of mass, or for practical purposes, in terms of weight, neither the convenience, nor the precision of which is in any serious doubt. Such procedure is especially allowable where, as in the human case, a certain change in mass at a particular stage of development calls for a corresponding change in length, though the relation between these changes is obviously not, nor does it need to be, uniform over the entire growth epoch

Metabolism or Basal Metabolism —This useful term has found and indeed in certain respects, deserves the numerous applications it already enjoys. When used alone, however, it refers in general to energy exchange and in particular to that portion of energy which is actually disbursed and can be measured in the form of heat by accepted modern methods of procedure. But heat production, in turn, has been, and in reality requires to be, treated in one of several ways. There are, as a matter of fact, three essentially different units in which heat production may be expressed and for purposes of clarity they are outlined briefly in Table II.

TABLE II

CLASSIFICATION OF BASAL HEAT PRODUCTION

TYPE	UNIT
1 Cumulative Heat 2 Rate of Heat Production 3 Rate of Heat Production per unit of size, 1e, True Metabolism	Calories* Calories per dav Calories per Kg per dav

<sup>\*</sup>The large or Kg Calorie

The term metabolism, if it is to be useful at all, can obviously not apply to each and every one of these three units of heat output in clusively, primarily because it is intended, whether so expressed or not, to convey a decidedly more restricted and definite impression than that contained in the comprehensive phrase "heat production" Consequently, in order to avoid misunderstanding, it is suggested that the unit of heat production given in item 3 of the table, be accepted as defining the term metabolism when the latter is used alone in connection with basal heat production

Thus, so long as mass is chosen in place of length as the more ap propriate measure of size in dealing with growth, it is correspondingly preferable in the case of human metabolism to employ the unit ex pressed in Calories per hag per day rather than to turn obliquely away from the original scheme of things in order to record heat output in terms of surface area The latter method has been, and continues to be, widely employed in practice, chiefly on the basis of a long and truly serviceable tradition. But it possesses indubitably the serious disadvantage of propagating the entirely false impression that sur face area bears a direct causal relationship to heat production the extensive discussions which have appeared on the subject arguments pro and con have been presented with equal fervor, though it is quite immaterial whether surface, mass, or even length are employed as the base of reference, since all of these are explicitly connected by means of the property of matter, called density The latter, as D E Zook has recently shown, remains sufficiently constant throughout life to be treated so. Besides the transformation from Cal /Kg /Day to Cal /sq.M /Day is a perfectly simple procedure, and the formulas of Mech, Lussauer and of others as well as any success to which they are entitled to lay claim depend though the fact is not everywhere recor nized, upon the form of this fundamental physical relationship of mass length and density But so long as mass is the unit of choice in the matter of growth-so long as growth itself is dynamically responsible for the peculiarities of heat production in infants and children, and so long as it is held desirable to determine the quantity of heat rela tive both to size and to time-there is to be consistent, more reason to express the results with reference to weight than to surface area, even though weight must be acknowledged to vary' more widely than body surface when individual children are compared

It is indeed on just the latter account that standardization on the basis of surface has found much of its favor in modern practice. Now, in view of the physical relations already noted, a given change in mass is bound to be accompanied by a comparatively small change in body surface density remaining the same, whence it is clear that measurements referred to surface as a standard must in the nature of things be expected to appear more uniform and therefore less irregu

lates to the several forms in which energy is disbursed during the process of growth, the second to the matter of defining the sense with which the term maintenance is employed

So far as the former of these two points is concerned, it may be seen from the chart that the energy supplied for growth is held to be distributed and utilized in five essentially different ways cells, (2) storage, (3) momentum, (4) dissipation, and finally (5) in the process of synthesis or cellular proliferation, the subjoined char acters  $V_c$ ,  $\kappa$ ,  $\lambda$ ,  $\rho$ ,  $E_c$ , denoting respectively the several terms in the original nal equations of growth and metabolism3 that are concerned with the energy partition just mentioned \* But it is also important to know, even from the clinical side of the matter, that these symbols represent in reality, certain fundamental properties of growth, or perhaps bet ter, of the entire system which is undergoing growth but one example, the symbol p represents what we have termed the resistance to growth. It is associated, in virtue of this property with energy that is dissipated during the process of reduplication, by which we mean that such energy cannot be recovered to do any further work of growth Energy so consumed moreover is ultimately liberated in the form of heat and it becomes, as a result, a major factor in the mat ter of metabolism Thus, as the chart indicates, the resistance  $\rho$  con stitutes one of the main connecting links between the events of pure growth on the one hand and heat production on the other

But an even more important leason why it is necessary to take cognizance of this and of the other symbols is that no satisfactory understanding of growth can be obtained until we are informed pre cisely how any factor known to affect growth itself, likewise and in turn operates on the various properties of the system schematically arranged and symbolized in the figure It is evident therefore that growth is insufficiently described, or understood, by merely detailed successive changes of size with respect to age Accordingly, to get to the bottom of things we shall need to learn not only that some substance, x say, "promotes" or "fails to promote" growth, but we shall actually be required to find out precisely how this substance or factor x affects each of the foregoing fundamental properties of growth To collect this information it is necessary, as the present scheme briefly suggests, simply to study growth on the one hand with concomitant heat production on the other Such problems, of course are quite definitely a matter of further research, yet, it seems logical that those who are intimately and primarily concerned with hum growth should also be made aware of their importance

Energy of Maintenance—It has been the custom of pediatrists speak broadly of the maintenance requirement as that quantity

<sup>\*</sup>A further description of the above symbols as well as a synopsis of other immental quantities entering the equations of motion appears in a current paper ?

cause size, either as weight or surface enters the equations of metabolism in such a way as to affect the end results adversely. Greater uniformity is not only to be expected in, but is actually displayed by, observations on heat production which are expressed in the simpler unit of Cal/Day. The latter phenomenon is of particular interest here because it can be strikingly demonstrated in data on the heat production of infants and young children

#### THE SCHEME OF ENERGY EXCHANGE FOR GROWTH AND METABOLISM

Having thus considered a number of the more important propositions that are fundamentally in the background of any discussion on

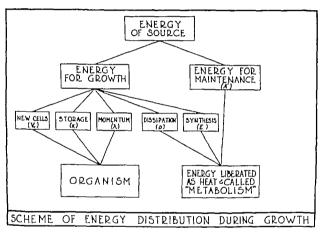


Fig 1

human growth, it will be useful to outline briefly the scheme of energy exchange by means of which it is possible more clearly to understand many otherwise occult phenomena of growth itself, and upon which in terms of our own analysis, the dynamical connection between growth and metabolism may be said to rest. The procedure itself is simple and is illustrated diagrammatically in Fig. 1. It is based primarily upon the fundamental assumption quite easily justified by the conservation law, that an infant let us say in the basal state requires energy for the dual purpose of growth and maintenance alone. There are two respects in which this scheme differs from previous interpretations and special emphasis needs for the sake of clarity to be placed upon them here. The first as is obvious from the figure re

lates to the several forms in which energy is disbursed during the process of growth, the second to the matter of defining the sense with which the term maintenance is employed

So far as the former of these two points is concerned, it may be seen from the chart that the energy supplied for growth is held to be distributed and utilized in five essentially different ways cells, (2) storage, (3) momentum, (4) dissipation, and finally (5) in the process of synthesis or cellular proliferation, the subjoined characters  $V_c$ ,  $\kappa$ ,  $\lambda$ ,  $\rho$ ,  $E_c$ , denoting respectively the several terms in the original equations of growth and metabolism3 that are concerned with the energy partition just mentioned \* But it is also important to know, even from the clinical side of the matter, that these symbols represent in reality, certain fundamental properties of growth, or perhaps better, of the entire system which is undergoing growth but one example, the symbol  $\rho$  represents what we have termed the resistance to growth. It is associated, in virtue of this property with energy that is dissipated during the process of reduplication, by which we mean that such energy cannot be recovered to do any further work Energy so consumed moreover is ultimately liberated in the form of heat and it becomes, as a result, a major factor in the mat-Thus, as the chart indicates, the resistance  $\rho$  conter of metabolism stitutes one of the main connecting links between the events of pure growth on the one hand and heat production on the other

But an even more important reason why it is necessary to take cognizance of this and of the other symbols is that no satisfactory understanding of growth can be obtained until we are informed precisely how any factor known to affect growth itself, likewise and in turn operates on the various properties of the system schematically arranged and symbolized in the figure It is evident therefore that growth is insufficiently described, or understood, by merely detailing successive changes of size with respect to age Accordingly, to get to the bottom of things we shall need to learn not only that some substance, x say, "promotes" or "fails to promote" growth, but we shall actually be required to find out precisely how this substance or factor x affects each of the foregoing fundamental properties of growth To collect this information it is necessary, as the present scheme briefly suggests, simply to study growth on the one hand with concomitant heat production on the other Such problems, of course, are quite definitely a matter of further research, yet, it seems logical that those who are intimately and primarily concerned with human growth should also be made aware of their importance

Energy of Maintenance —It has been the custom of pediatrists to speak broadly of the maintenance requirement as that quantity of

<sup>\*</sup>A further description of the above symbols as well as a synopsis of other fundamental quantities entering the equations of motion appears in a current paper.

energy necessary at any stage of infancy or childhood to prevent loss of body weight, and consequently as that quantity sufficient for all purposes (including activity and waste) other than that of growth itself. Now, discounting the fractions recently classified as "super metabolism," i.e., food, activity and temperature, a similar interpretation can be made to apply to the basal state. Consequently, since basal metabolism (Cal/Kg/Day) is actually higher in infancy than in childhood, it is clear that maintenance needs" in the sense described above, will likewise decline as ago advances and as the "impetus" of growth becomes less. On a comparative basis an older child in the basal state will therefore require less energy than an infant to keep from losing weight. This particular interpretation of "main tenance" fills a useful place in practice but it has been found neces sary, in dealing with growth and metabolism from the dynamic point of view, to look upon this question of maintenance somewhat differently

True maintenance from the latter standpoint, can and should be held to apply only to tissue that is physiologically at rest, and that is to tissue in a state of pure and simple existence. Thus, tissue which 18 in a state of growth is not considered as being 'at rest' it is, as a matter of fact, "in the motion of growth," though quite evidently, just as much in need of being nourished as though it were not. Its energy requirement will, obviously, and for the reason just mentioned be more than that of an equal quantity which remains 'at rest' and it is evident, therefore, that maintenance so defined refers solely to the quantity of energy required to keep the cells in nutritional equi The proposition here involved could be put forth in another way by stipulating that comparisons of maintenance energy should be calculated for tissues in the same state of activity whence for obvious reasons, it would be simplest to select the state of 'rest' as the most suitable base of comparison. Thus, basal heat output well known to be high in infancy and throughout childhood we shall con sider high solely because it is generated by tissue which is naturally In a different state of activity at this than at a later stage of life. and the difference will be held to the account of growth itself. These relationships are most simply portrayed by means of the self-explana tory scheme already presented in Fig 1

From this it is clear first that basal heat production in growing subjects must always exceed that of subjects in whom growth has ceased and second that the comparatively higher metabolism and the relatively greater energy requirement of healthy infants and children is due and due only to the fact that they are immersed in the flux of growth

It may finally be understood on the basis of the present conception of growth and from the foregoing definition of maintenance how the restriction of food to the level of maintenance requirements alone (25 34 Cal /Kg /Day) will necessarily be followed by a course of swift and unescapable loss of weight in a subject undergoing growth, and how, on the contrary, another subject who has come to the stage of adult equilibrium and is given an equivalent quantity of food, will incui no loss at all

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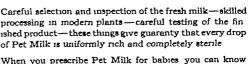
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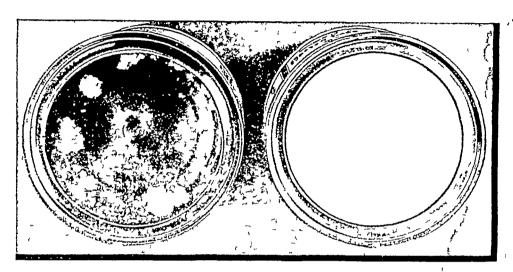
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